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CHANGES IN THE LIVER PRODUCED BY CHRONIC PASSIVE CONGESTION

WITH SPECIAL REFERENCE TO THE PROBLEM OF CARDIAC CIRRHOSIS

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In cases of congestive heart failure, varying degrees of passive congestion of the liver universally occur from the resulting stasis in the portal circulation. Chronic passive congestion of the liver becomes evident when heart failure becomes protracted or frequently recurrent. At times the liver increases enormously in size, so that it reaches the level of the umbilicus or even lower. Not infrequently the degree of portal stasis is disproportionate to the stasis in the systemic circulation, probably owing to the fact that a greater degree of obstruction to the blood flow from the hepatic veins occurs than to that in the inferior vena cava. Likewise, the capillaries of the portal system are possessed of a relatively high degree of permeability.

The effects of chronic passive congestion on the liver have been the subject of much controversy for nearly a century, the issue involved chiefly concerning the production of hepatic cirrhosis. Becquerel,[1] in 1840, was the first to express the opinion that chronic passive congestion resulting from cardiac failure produces hepatic cirrhosis. The influence of his work was quite far reaching and fostered adoption of the term *cirrhose cardiaque*. This belief received the support of Rokitansky [2]

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The pathologic investigation in this study was made by Dr. Boland under the direction of Dr. H. E. Robertson, of the Section on Pathologic Anatomy, the Mayo Foundation, in partial fulfilment of the requirements for the degree of Master of Science in Medicine. Clinical correlations and the discussion, together with reorganization of the material, are the work of Dr. Willius.

1. Becquerel, A.: Recherches anatomico-pathologiques sur la cirrhose du foie, Arch. gén. de méd. **53**:40-79 (May) 1840.

2. Rokitansky, C.: A Manual of Pathological Anatomy, London, C. & J. Adlard, 1849, vol. 2.

(1849) and Henle[3] (1844). Budd[4] (1857) observed that the size of the liver in certain cases of chronic valvular disease was decreased, but he was unwilling to accept this as the result of heart failure alone. He stated the belief that these changes in the liver occur only in cases in which spirits have been used excessively and that these indiscretions increase the vulnerability of the organ to the influences of chronic stasis. Budd's views were championed by Monneret[5] (1852) and by Bamberger[6] (1855). The literature of the ensuing years contained many conflicting opinions.[7]

In 1883 Sabourin[8] published his classic work on chronic passive congestion of the liver. He clearly implied that he favored the concept that hepatic cirrhosis results from cardiac failure. He found that the degenerative processes as they occur in cases of chronic congestive heart failure result in capillary dilatation and trabecular atrophy. It was in these zones of atrophy about the central vein that he found the new connective tissue to be formed first. He said he believed that the sequence of events leading to sclerosis depends on a thickening and contraction of the strands of connective tissue which line the spaces about the central veins, this thickening and condensation eventually leading to the stage of central cirrhosis. He stated that this type of cirrhosis is easily recognizable, because it connects central vein to central vein or sublobular vein and thus encircles the hepatic tissue of the peripheral portion of adjacent lobules. Such an arrangement produces an apparent reversal of the usual order, the portal system at times being in the center of the lobule. Sabourin's views on the pathogenesis of these changes are well exemplified in the following quotation:

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3. Henle, cited by Rolleston, H., and McNee, J. W.: Diseases of the Liver, Gall-Bladder and Bile-Ducts, New York, The Macmillan Company, 1929.

4. Budd, G.: On Diseases of the Liver, ed. 3, Philadelphia, Blanchard & Lea, 1857.

5. Monneret, cited by Piéry.[10h]

6. Bamberger, cited by Piéry.[10h]

7. (*a*) Cornil, V., and Ranvier, L.: A Manual of Pathological Histology, translated by E. O. Shakespeare and J. H. C. Simes, Philadelphia, Henry C. Lea, 1880. (*b*) Ferricks, cited by Piéry.[10h] (*c*) Förster, cited by Piéry.[10h] (*d*) Frerichs, F. T.: A Clinical Treatise on Diseases of the Liver, London, The New Sydenham Society, 1861, vol. 2. (*e*) Green, T. H.: An Introduction to Pathology and Morbid Anatomy, ed. 5, Philadelphia, Henry C. Lea's Son & Co., 1884. (*f*) Jones, H., cited by Talamon.[7m] (*g*) Klebs, cited by Talamon.[7m] (*h*) Legg, W., cited by Talamon.[7m] (*i*) Liebermeister, cited by Piéry.[10h] (*j*) Murchison, C.: Clinical Lectures on Diseases of the Liver, Jaundice and Abdominal Dropsy, ed. 3, London, Longmans, Green & Co., 1885. (*k*) Rendu, cited by Piéry.[10h] (*l*) Rindfleisch, cited by Talamon.[7m] (*m*) Talamon, C.: Contribution à l'étude de la sclérose hépatique d'origine cardiaque, Rev. de méd., Paris **1**:273-296, 1881.

8. Sabourin, C.: La cirrhose du système sus-hépatique d'origine cardiaque, Rev. de méd., Paris **3**:521-535, 1883.

It is sufficient for us to know that there is blood stagnation produced by cardiac affliction and that this stagnation produces capillary trabecular atrophy and finally sclerosis, and all in a very systematic manner prevailing over the hepatic venous territory, such as we understand it.

Parmentier,[9] in 1889, reported the first experimental work on chronic passive congestion of the liver. He produced chronic engorgement of the liver in animals by bringing about tricuspid regurgitation. He was not, however, able to produce hepatic cirrhosis in his experimental animals by this method. The contemporary literature contains other references antagonistic to the tenets of the existence of cardiac cirrhosis.[10]

Lambert and Allison,[11] in 1916, reviewed 112 cases of chronic passive congestion of the liver. They divided their cases according to five types as follows: In the first type there was principally capillary dilatation with atrophy of the central cells; in the second type, central degeneration with or without congestion; in the third type, a central accumulation of fat with midzone hyperemia or necrosis; in the fourth type, what was described as central necrosis, usually associated with hemorrhages, and in the fifth type, "collapse fibrosis," a condition which they concluded was identical with cardiac cirrhosis. Of the last type of case they found reports of only 16 instances (14.2 per cent), the condition occurring only in the presence of chronic heart failure.

Ophüls,[12] in 1926, found in 166 cases of cirrhosis of the liver occurring in 3,000 necropsies only 22 in which the condition was typical of cardiac cirrhosis; this represents an incidence of about 0.7 per cent.

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9. Parmentier, cited by Rolleston, H., and McNee, J. W.: Diseases of the Liver, Gall-Bladder and Bile-Ducts, New York, The Macmillan Company, 1929.

10. (*a*) Bolton, C.: The Pathological Changes in the Liver Resulting from Passive Venous Congestion Experimentally Produced, J. Path. & Bact. **19**: 258-264, 1914-1915. (*b*) de Sévedavy, J., cited by Piéry.[10h] (*c*) Frothingham, C., Jr.: Cronic Passive Congestion of the Liver, Arch. Int. Med. **5**:1-5 (Jan.) 1910. (*d*) Hanot, V.: La cirrhose hypertrophique avec ictère chronique, Paris, Rueff & Cie, 1892; (*e*) La cirrhose de Budd, Arch. de méd. **1**:3-20, 1899. (*f*) Hutchison, R., and Levy Simpson, S.: Occlusion of the Hepatic Veins with Cirrhosis of the Liver, Arch. Dis. Childhood **5**:167-186 (June) 1930. (*g*) Oertel, H.: Multiple Non-Inflammatory Necrosis of the Liver with Jaundice in Chronic Cyanosis, Arch. Int. Med. **6**:293-300 (Sept.) 1910. (*h*) Piéry, M.: Pathogénie de la cirrhose cardiaque: Stase sanguine et sclérose du foie, Arch. gén. de méd. **2**:582-613 and 714-744, 1900. (*i*) Rössle, R., cited by Albot, G.: Hépatites et cirrhoses: Classification, pathogénèse et morphogénèse des hépatites diffuse aiguës, subaiguës et chroniques d'après les notions récentes sur la physio-pathologie hépato-biliaire, Paris, Masson & Cie, 1931. (*j*) Salaman, R. N.: The Pathology of the Liver in Cardiac Disease and Its Clinical Lessons, Lancet **1**:4-7 (Jan. 5) 1907.

11. Lambert, R. A., and Allison, B. R.: Types of Lesion in Chronic Passive Congestion of the Liver, Bull. Johns Hopkins Hosp. **27**:350-356 (Dec.) 1916.

12. Ophüls, W.: A Statistical Survery of Three Thousand Autopsies, Stanford University, Calif., Stanford University Press, 1926.

He defined cardiac cirrhosis as "advanced cyanotic atrophy of the liver with development of considerable new fibrous tissue."

Moschcowitz,[13] in 1937, advanced the idea that cirrhosis of the liver occurring with chronic heart failure is the result of increased venous pressure within the hepatic area.

In 1930 Zimmerman and Hillsman[14] published convincing experimental data indicating that hepatic cirrhosis may result from severe chronic passive congestion. They produced partial obstruction of the thoracic portion of the inferior vena cava in dogs by means of an aluminum band.

Boles and Clark,[15] in 1936, found hepatic cirrhosis of all types in 6 per cent of 4,000 necropsies and stated that cardiac cirrhosis was the third most common type.

The present day French view of *cirrhose cardiaque* was expressed as follows by Roussy, Leroux and Oberling[16] in 1933:

> If the process of chronic passive congestion is prolonged, the picture becomes complicated by a process of regeneration of hepatic tissue which progresses to the production of exuberant nodules, and an adenomatous appearance is produced. By proliferation of connective tissue about the central lobular vein and around the hypertrophic islands of tissues, the surface becomes irregularly granular and hardened. The liver shrinks. On macroscopic section the area is separated cleanly into pale yellow regions on a background of liver, which is hardened and congested. That lesion corresponds to the *cirrhose cardiaque*.

Roussy and his associates emphasized the fact that there are two primary views regarding the pathogenesis: One considers venous stagnation as the etiologic agent, and the other considers additional influences, such as infection and toxemia, as the etiologic agent.

MATERIAL

The basis of this study was 75 cases of cardiac disease in which prolonged single or multiple episodes of congestive heart failure had occurred. Cases of congestive failure of short duration were excluded, as cardiac cirrhosis is not encountered in such instances. This fact was determined in a review of 500

13. Moschcowitz, E.: Hypertension of the Pulmonary Circulation: Its Causes, Dynamics and Relation to Other Circulatory States, Am. J. M. Sc. **174**: 388-406 (Sept.) 1927; Phlebosclerosis of the Hepatic Veins as Associated with Chronic Passive Congestion of the Liver and Cardiac Cirrhosis (Preliminary Report), in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman, New York, International Press, 1932, vol. 2, pp. 857-875.

14. Zimmerman, H. M., and Hillsman, J. A.: Chronic Passive Congestion of the Liver: An Experimental Study, Arch. Path. **9**:1154-1163 (June) 1930.

15. Boles, R. S., and Clark, J. H.: The Rôle of Alcohol in Cirrhosis of the Liver: A Clinical and Pathological Study Based on Four Thousand Autopsies, J. A. M. A. **107**:1200-1203 (Oct. 10) 1936.

16. Roussy, G.; Leroux, R., and Oberling, C.: Préces d'anatomie pathologique, Paris, Masson & Cie, 1933, vol. 1.

unselected cases (Dr. Boland[17]) of chronic passive congestion of the liver. Microscopic studies of the liver were made in each case by one of us (Dr. Boland), sections being stained with hematoxylin and eosin and by the Van Gieson method. Many sections were also stained by the Mallory-Heidenhain and Perdrau technics.

Edema of the dependent portions of the body was necessary before the patient was considered as having congestive heart failure. The onset of failure was determined as accurately as possible from the first appearance of the edema (table 1).

Most of the principal forms of heart disease were represented in the etiologic array responsible for the congestive heart failure (table 2).

TABLE 1.—*Single and Multiple Episodes of Congestive Heart Failure*

Single Episode; Duration of Failure, Months	No. of Cases
4- 5	13
6- 7	13
8- 9	8
10-11	2
12+	11
Total	47
Multiple Episodes; Number of Episodes	
2-4	17
5+	11
Total	28

TABLE 2.—*Causes of Congestive Failure*

	No. of Cases
Hypertensive heart disease	33
Coronary and hypertensive heart disease	1
Hypertensive heart disease and coronary thrombosis	5
Hypertensive heart disease and exophthalmic goiter	1
Severe coronary sclerosis with extensive myofibrosis	3
Coronary thrombosis	2
Rheumatic mitral stenosis (with or without mitral insufficiency)	10
Rheumatic mitral stenosis with defects of aortic valve	4
Rheumatic mitral stenosis with defects of aortic and tricuspid valves	1
Rheumatic mitral stenosis with adherent pericarditis	1
Rheumatic tricuspid stenosis	1
Calcareous (rheumatic) aortic stenosis	4
Adherent pericarditis	1
Syphilitic aortitis and aortic insufficiency; aneurysm	3
Pulmonary emphysema	3
Patent foramen ovale (huge)	2
Total	75

The ages of the patients ranged from 5 to 85 years, the average age being 55.6 years. Eighty-seven per cent of the patients were between the ages of 40 and 70. There were 56 males and 19 females, a ratio of 3:1.

The clinical history, physical findings, hospital records and laboratory data were studied in each case, and an attempt was made to correlate these findings with the pathologic changes in the liver.

GROSS FINDINGS

Ascites occurred in 89.3 per cent of the cases in which there was a single episode of congestive heart failure and in 82.1 per cent of those

17. Boland, E. W.: Unpublished data.

in which there were multiple episodes. The incidence of acites in the whole group was 86.6 per cent. Icterus was present at some time during the attack of failure in 12.7 per cent of the cases in which there was a single episode and in 17.8 per cent of those in which there were repeated episodes of cardiac failure. The incidence of icterus in the entire series was 14.6 per cent.

The average weight of the liver in cases of one protracted episode of congestive heart failure was 1,799 Gm., the estimated normal weight for this group being 1,764 Gm. The average weight of the liver in cases of recurrent attacks was 1,608 Gm., the estimated normal for this group being 1,674 Gm.

HISTOPATHOLOGIC OBSERVATIONS

According to the histopathologic observations the cases may be classified in three general groups: (1) a group of cases in which there was atrophy or necrosis or both in the hepatic lobule without evidence of condensation of reticulum or cirrhosis, (2) a group of cases in which there was atrophy or necrosis together with condensation of reticulum and thickening but without cirrhosis and (3) a group of cases in which there was actual hepatic cirrhosis.

Group 1.—Thirty-seven (49 per cent) of the 75 cases belonged in the first group (table 3). The microscopic changes in these cases were similar to those generally described as occurring in chronic passive congestion of the liver. The atrophy or necrosis was always most marked in the central third of each hepatic lobule, especially immediately adjacent to the central vein. The degeneration decreased in degree toward the periphery of the lobule. In some cases a variable degree of necrosis was apparently superimposed on the atrophic cells of the central portion of the lobule. When necrosis predominated in the central portion of the lobule, the hepatic cells surrounding the necrotic area usually showed some degree of atrophy. In many cases the degeneration extended from central vein to central vein, giving the appearance of reversed lobulation. The degree of degeneration was variable. In 6 cases there was only a minimal amount of central atrophy. In 26 cases there was a moderate to marked degree of atrophy in the central third of the lobule, with a decreasing amount of atrophy in the middle and peripheral zones. Marked necrosis of the central cells with atrophy in the peripheral cells was present in 3 cases. In 7 cases there was marked atrophy of the cells of the central portion of the lobule, with superimposed necrosis (fig. 1).

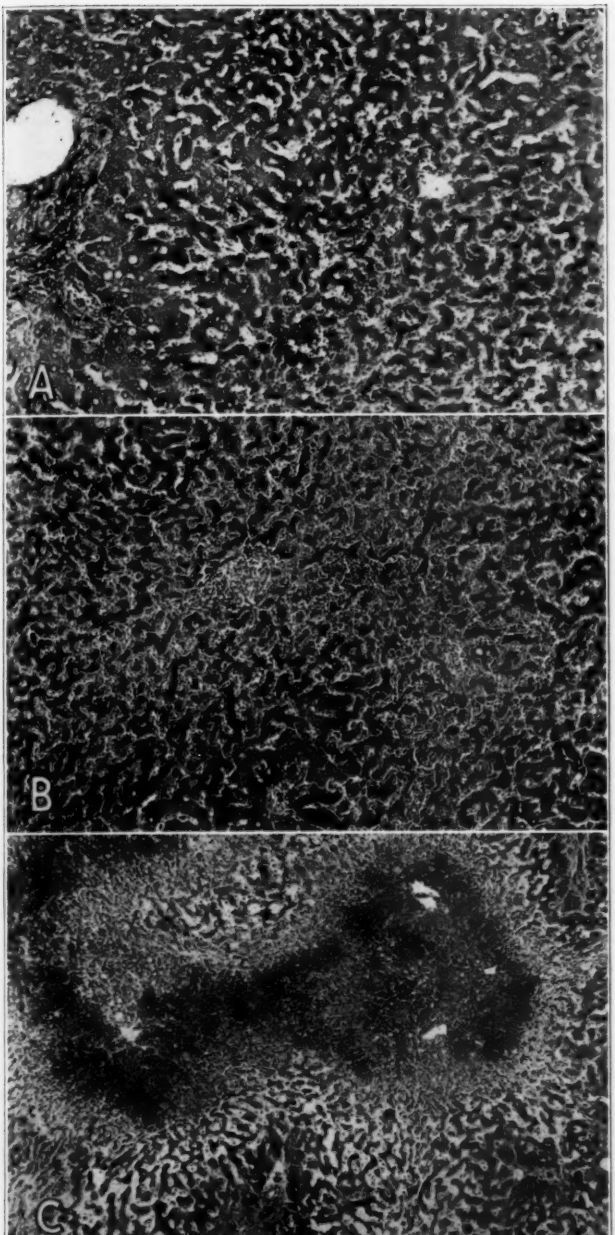

Fig. 1.—Atrophy or necrosis without condensation of reticulum or cirrhosis. *A*, a mild degree of central atrophy; *B*, a moderate degree of central atrophy, and *C*, severe central necrosis.

Group 2.—The second group consisted of 33 cases (44 per cent). In these there was evidence of condensation of reticulum in the degenerated areas (table 4). This condensation was always most marked in the degenerated areas and seemed to vary proportionately to the degree of degeneration present. However, as was observed in the preceding group, marked degeneration might occur without a condensation of reticulum. The condensation appeared to result from the collapse of the central portion of the lobule as a result of the destruction of the

Table 3.—*Group 1: Cases in Which There Was Atrophy or Necrosis or Both in the Hepatic Lobules Without Other Changes*

Single Episode; Duration of Failure, Months	No. of Cases
4- 5	6
6- 7	9
8- 9	6
10-11	2
12+	9
Multiple Episodes (Number)	
2-4	3
5+	2
Total	37 (49% of series)

Table 4.—*Group 2: Cases in Which There Was Atrophy or Necrosis Together with Condensation and Thickening of Reticulum*

Single Episode; Duration of Failure, Months	No. of Cases
4- 5	6
6- 7	4
8- 9	1
10-11	0
12+	2
Multiple Episodes (Number)	
2-4	11
5+	9
Total	33 (44% of series)

hepatic cells in that region. Close observation of the reticulum fibers revealed that they actually appeared thicker than normal. This was particularly well shown when the sections were stained by the Van Gieson and Perdrau methods. Reverse lobulation to some degree could be demonstrated in every case in this group. The reverse arrangement was most distinct in cases of pronounced condensation of reticulum. In some regions the condensed reticulum extended so distinctly from central vein to central vein that a definite band of fibers could be seen surrounding the peripheral zones of the remaining hepatic tissue, a portal radicle being located in the center of this apparently reversed lobule.

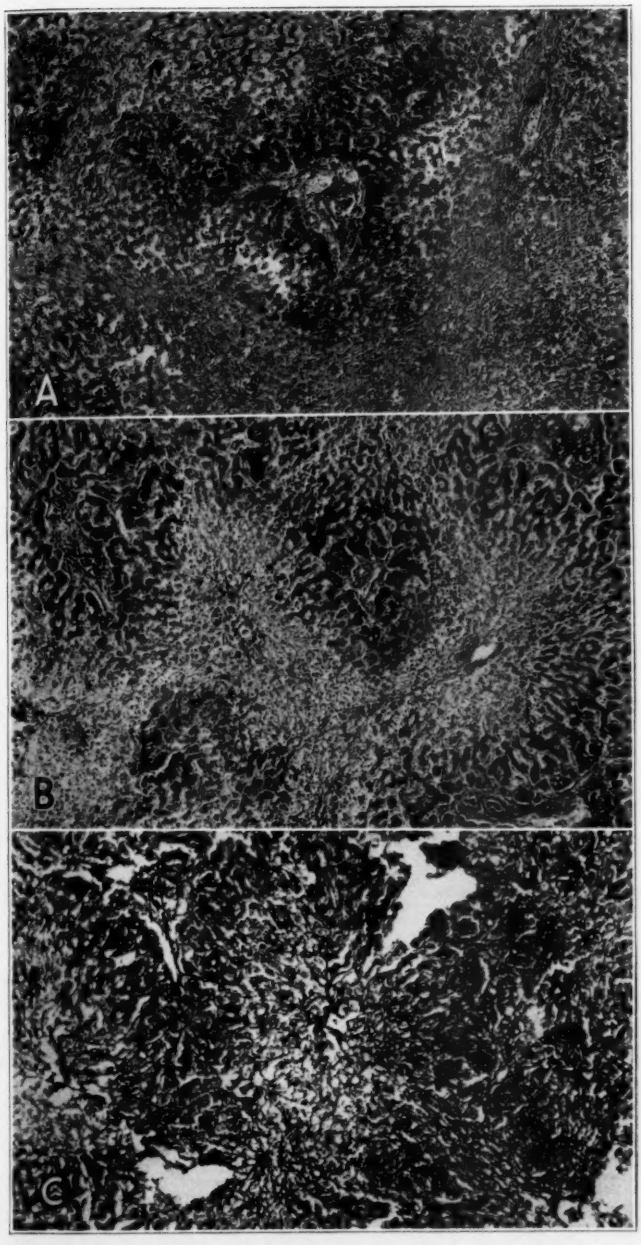

Fig. 2.—Condensation and thickening of reticulum but without cirrhosis. *A*, a mild degree of condensation of reticulum (hematoxylin and eosin stain); *B*, a moderate degree of condensation of reticulum (note the reversed lobulation and thickening of reticulum [Van Gieson stain]), and *C*, a moderate degree of condensation and thickening of reticulum (Perdrau stain).

The degree of condensation and thickening of the reticulum varied in this group. In 21 cases the condensation was not pronounced, in 7 cases it was moderate and in 5 cases it was marked. Cases of moderate and marked degrees of condensation would probably be classified by some investigators as cases of cardiac cirrhosis. However, with careful study of the sections, no fibrous tissue proliferation was found but rather only condensation and thickening of preexisting reticulum fibers. For this reason, such cases should be designated as demonstrating condensation of reticulum resulting from chronic passive congestion rather than being classified as cases of true cirrhosis (fig. 2).

GROUP 3.—In 5 cases (7 per cent) of the series there was true hepatic cirrhosis (table 5).

In these 5 cases there were marked degeneration of the central portion of the lobules and condensation of reticulum. Reversed lobulation

TABLE 5.—*Group 3: Cases of True Hepatic Cirrhosis as a Result of Cardiac Decompensation*

Single Episode; Duration of Failure, Months	No. of Cases
4- 5	1
6- 7	0
8- 9	1
10-11	0
12+	0
Multiple Episodes (Number)	
2-4	2
5+	1
Total	5 (7% of series)

was prominent. There appeared to have been almost complete destruction of entire lobules in certain scattered areas. Extensive collapse of the necrotic regions evidently occurred, and portal radicles appeared to have been caught in the massive coalescence. In these regions fibrous tissue proliferation had occurred, and fibroblasts could be identified by the oil immersion method. In addition, the normal architectural arrangement of the liver was disrupted, and an increase in the number of lymphocytes was seen in some of the fibrotic areas. An apparent increase in the number of bile ducts was frequently observed. In 3 of the 5 cases there appeared to be adenomatous regeneration of hepatic tissue. The cirrhosis in these cases was not uniform throughout the sections but was scattered in an irregular manner. Between the areas of fibrosis the hepatic substance demonstrated central lobular degeneration, condensation of reticulum and reversed lobulation. At times the bands of condensed reticulum could be seen to join the areas of fibrosis. Indeed, it appeared that entire lobules had degenerated and collapsed in some regions and that these areas served as sites for the proliferation

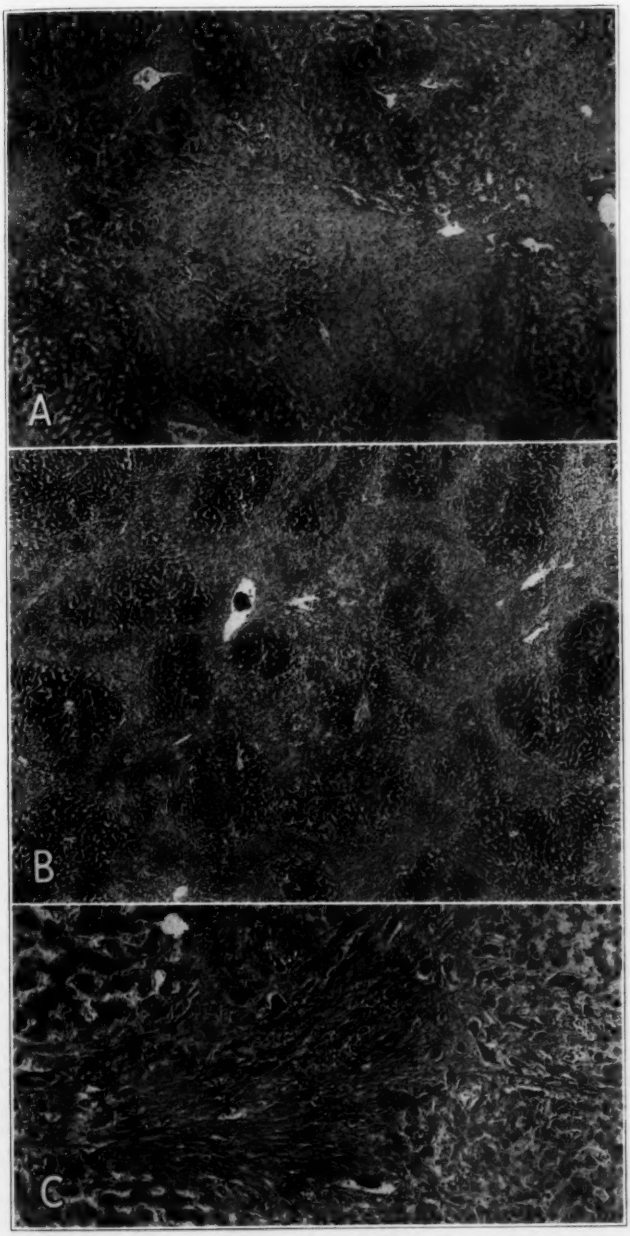

Fig. 3.—True cirrhosis. *A*, an area of fibrosis with an apparent increase in the number of bile ducts (note the reversed lobulation and the condensation of reticulum in the adjacent tissue [hematoxylin and eosin stain]); *B*, lower magnification, showing marked condensation of reticulum, reversed lobulation and fibrosis of the areas of massive destruction (hematoxylin and eosin stain), and, *C*, a higher magnification of the preceding section, showing fibrosis and an increase in the number of bile ducts (Van Gieson stain).

of fibrous tissue. The patchy nature of the fibrosis and the intervening regions of central degeneration and condensation of reticulum made the picture differ considerably from that usually seen in advanced portal cirrhosis.

In 1 additional case there was failure to show marked central destruction of the lobules, with reticular condensation and reversed lobulation. There was, rather, only a mild degree of central atrophy in lobules which persisted between the scattered areas of fibrosis. As will be pointed out later, in this case there were certain clinical features which indicated that the hepatic cirrhosis probably preceded the onset of congestive heart failure (fig. 3).

COMMENT

The most frequent pathologic picture seen in the liver as a result of prolonged or repeated episodes of congestive heart failure is degeneration of the central portion of the lobules, with or without condensation of reticulum. True hepatic cirrhosis is an uncommon finding.

It is generally assumed that central lobular atrophy results from chronic passive congestion of gradual onset and that necrosis develops when cardiac failure occurs more abruptly or is of greater severity. It was difficult to establish this fact from this material; it may be suggested, however, that when necrosis was apparently superimposed on preexisting central atrophy, the patient may have suffered severe terminal passive congestion. The toxic factor of Mallory [18] cannot be disregarded in these cases as the cause of the severe central necrosis. It must be pointed out, however, that the clinical record and associated postmortem observations do not correspond with sufficient regularity for the definite establishment of an infectious or toxic origin for the necrosis. It is a well known fact that many toxins exert their first visible effects on the central cells of the hepatic lobule. Bollman and Mann,[19] moreover,

18. Mallory, F. B.: Necrosis of the Liver, J. M. Research **6**:264-280 (July) 1901; Chronic Passive Congestion of the Liver, ibid. **24**:455-462 (April) 1911; cited by Boles and Clark.[15]

19. Bollman, J. L.: Experimental Cirrhosis of the Liver, Proc. Internat. Assemb. Inter-State Post-Grad. M. A., North America, 1929, pp. 387-390. Bollman, J. L., and Mann, F. C.: Alterations in Hepatic Function Produced by Experimental Hepatic Lesions, Ann. Int. Med. **9**:617-624 (Nov.) 1935. Bollman, J. L.; Mann, F. C., and Magath, T. B.: Studies on the Physiology of the Liver: XV. Effect of Total Removal of the Liver on Deaminization, Am. J. Physiol. **78**:258-269 (Oct.) 1926. Mann, F. C., and Bollman, J. L.: Jaundice: A Review of Some Experimental Investigations, J. A. M. A. **104**:371-374 (Feb. 2) 1935. Bollman, J. L., and Mann, F. C.: Experimentally Produced Lesions of the Liver, Ann. Int. Med. **5**:699-712 (Dec.) 1931.

have clearly shown that impairment of the circulation of the liver increases the effectiveness of many hepatic toxins. One cannot, therefore, deny the possibility of a coexisting toxic factor in these cases. That some factor besides passive congestion may be involved is suggested by the fact that one cannot predict from the clinical history and physical findings whether the liver will show atrophy or necrosis. The claim for the toxic factor becomes strengthened in some cases by the presence of many polymorphonuclear leukocytes in the necrotic areas. It must be remembered, however, that polymorphonuclear leukocytes may migrate to sites of necrosis regardless of its cause.

In 33 cases there was some degree of condensation of reticulum; it was minimal in 24 cases. In the remaining 9 cases the condensation was prominent, and several authors probably would have classified the cases as representing cirrhosis. These 9 cases corresponded well with the descriptions of cases of cardiac cirrhosis given by Sabourin, Salaman, Lambert and Allison, and Boles and Clark. They undoubtedly fit the descriptions of "red atrophy," "collapse fibrosis" and other terms used by some investigators as synonyms for cardiac cirrhosis. There was not, however, true cirrhosis as the term is generally understood. There were demonstrated only condensation and thickening of preexisting reticulum. In no case of this particular group was there evidence of new connective tissue proliferation, lymphocytic infiltration, adenomatous regeneration or an apparent increase in the number of bile ducts. In these cases the condition should therefore be designated as marked by condensation of reticulum and should not be included under the term cirrhosis.

It is interesting that some degree of condensation of reticulum and thickening was seen in 86 per cent of the cases of multiple episodes of congestive heart failure, whereas it occurred in only 30 per cent of the cases of protracted single episodes. The possibility that thickening of reticulum and perhaps some degree of condensation were residua of previous central degeneration becomes apparent. The thickening of reticulum may constitute the only irreversible change in the liver as a result of partial lobular degeneration resulting from chronic passive congestion. It is probable that during periods of congestive heart failure in cases in which there were repeated episodes of such failure the partially destroyed lobules regenerated almost to their normal state. Bollman and Mann have shown that if the necrosis of the lobule is not too extensive, reparative processes begin soon after removal of the toxin and that the restoration of the hepatic cells is so complete that the lobule again appears fairly normal. They said they believed that the disintegrated central hepatic cells are removed by phagocytosis, their place being taken by new hepatic cells. New cells appear to arise by division of adjacent uninjured hepatic cells. It may be emphasized

here that restoration to normal apparently does not occur when the necrosis involves an entire lobule.

In 6 of the 75 cases there was true cirrhosis. In 5 the changes differed from those of the advanced portal type as a result of their patchy nature and the central degeneration, condensation of reticulum and inverse lobulation in the hepatic parenchyma between the areas of fibrosis. In 5 of these 6 cases the cirrhosis evidently developed after the onset of congestive heart failure. In the sixth case the ascites appeared to follow a severe respiratory infection and began six months prior to the onset of dependent edema. It is assumed that in this case the cirrhosis preceded the onset of congestive heart failure. This supposition, as has already been shown, is strengthened by the microscopic observations.

It is reasonable to expect that cirrhosis which develops as a result of chronic passive congestion will be seen in those cases in which there have been repeated episodes of congestive heart failure. If the passive congestion is severe enough to produce necrosis of the hepatic cells, it is severe enough to prevent proliferation of fibrous tissue and adenomatous regeneration. Certainly, then, the cirrhosis must develop during periods of partial or complete restoration of cardiac function. In the 5 cases in this group, evidence seemed to be presented in support of this hypothesis. In 3 cases there was a history of repeated bouts of congestive heart failure, with intervening periods of partial recovery; in the 2 remaining cases there was a single continuous episode of failure. In each instance, however, there was a history of intervals of rest in bed, with considerable improvement in the degree of cardiac decompensation.

On the basis of the experimental work of Bollman and Mann, together with the microscopic observations in these cases, it seems justifiable to postulate the mechanism involved in the production of cirrhosis. The degeneration resulting from chronic passive congestion of the liver appears to vary in its extent and severity in different lobules. Some lobules may be completely destroyed, whereas others show degeneration in only the central portion. As has already been emphasized, the partially destroyed lobules probably are repaired during intervals of improvement in cardiac function to a state closely approximating the normal, a thickened reticulum remaining as the only relic. When entire lobules are destroyed the change appears to be irreversible, and the microscopic observations certainly suggest that in some areas whole lobules have been completely destroyed. In these extensively degenerated regions a collapse of the reticulum apparently has occurred. One or more portal spaces are frequently seen in the coalesced masses of reticulum. It is in these patchy areas that fibrous tissue proliferation and, at times, adenomatous regeneration of hepatic cells are observed. Bollman and Mann, in their report of cases of experimental cirrhosis,

suggested that the fibrous tissue develops from that already present about the portal spaces. This may likewise be the source of the fibrosis in these cases. The adenomatous regeneration probably proceeds from the few hepatic cells remaining in the collapsed lobules. It is conceivable, therefore, that during the intervals of partial cardiac recovery, fibrosis occurs in the areas of complete lobular destruction. In the partially destroyed lobules, reparation occurs which restores them to a state approaching normal.

The role played by toxins as a contributory agent in the production of cirrhosis is as obscure as in the cases of necrosis alone. In 1 of these 5 cases there was a history of acute catarrhal icterus which had occurred shortly before the appearance of dependent edema. Congestive heart failure in another case occurred in association with syphilitic aortitis and aneurysm. In this case a course of antisyphilitic treatment had been completed just prior to the first appearance of congestive heart failure. In the other 3 cases there was no evidence of a toxic or infectious factor.

Grossly, in 3 of the 5 cases in this group the cirrhotic liver was described as being nodular and firm. In the 2 remaining cases there were typical mottling of the "nutmeg" type and increased resistance to cutting.

Little correlation was found between the clinical history and the microscopic observations in this series of 75 cases. Ascites was present in each case of cirrhosis, but it was also found in 86.6 per cent of the entire series. Icterus was observed in 1 of the 5 cases of cirrhosis, although it occurred in 14.6 per cent of the entire series. When portal stasis is marked and engorgement of the liver occurs, jaundice not infrequently becomes evident in congestive heart failure and when associated with existing cyanosis results in a glaring and peculiar color of the skin and mucous membranes. Obviously neither ascites nor icterus can then serve as a diagnostic criterion of cirrhosis.

Hepatic function tests were made in only 3 of the 75 cases, a number too few to allow correlation. However, numerous tests have been carried out in other cases. In these cases either temporary recovery occurred or postmortem examination was not permitted. These observations indicate the fact that marked degrees of impairment of hepatic function, as expressed by the retention of dye introduced into the blood stream, are extremely uncommon. By denoting the grades of dye retention on a numerical basis (that is, grades 0 to 4) it is found that in the majority of cases retention is of grade 1 and in a smaller group of grade 2; with few exceptions higher grades of dye retention are not encountered. We are led to believe that functional impairment of the liver, as determined by laboratory methods, will for the most part serve as an index of the degree of necrosis or atrophy rather than as an index of the cirrhosis.

It is important to recall the fact that in some normal persons, especially those who are tall and slender, the edge of the liver may be palpated. Even though heart disease may exist in such cases, this finding may not indicate the presence of chronic passive congestion. Supplementary evidence, such as the presence of dyspnea, cyanosis, signs of pulmonary congestion and dependent edema, is usually requisite. It is also important to recognize the fact that the liver may become enlarged and varyingly engorged with blood in the absence of congestive heart failure. This is notably observed in some cases of pericardial effusion, particularly when the accumulation of fluid occurs rapidly and attains considerable proportions. This phenomenon is not the result of pressure downward from a fluid-laden pericardial sac but the result of compression of the orifices of the hepatic veins which open into the inferior vena cava. This appears to be caused by the accumulation of fluid in the pericardial sac, which rests on the diaphragm at the point where the inferior vena cava passes through.

When the liver becomes engorged rather rapidly, considerable persistent pain and local tenderness in the region of the organ are encountered. When the liver has had an opportunity to become adjusted to the circulatory stasis, as in cases of protracted congestive heart failure, these signs disappear.

Careful palpation of the liver in cases of chronic passive congestion usually gives important information; when there is massive ascites the examination obviously may reveal inconclusive findings. As a rule the enlarged liver is found to be firm, smooth and somewhat tender. When its surface is hard and irregular, it is almost certain that an additional condition exists, such as true portal cirrhosis or a metastatic malignant growth. Palpation, unfortunately, does not permit the positive identification of cardiac cirrhosis. The so-called pseudocirrhosis of Pick[20] will only be mentioned in passing. An enlarged, engorged liver that clearly pulsates is, with rare exceptions, evidence of organic changes involving the tricuspid valve.

Probably the most suggestive evidence available at this time in the clinical prediction that cardiac cirrhosis may be existent in a given case is through inference from the facts disclosed by this study. This evidence chiefly comprises the history of severe recurrent episodes of congestive heart failure over a relatively long time with intervals of improvement in cardiac function, when the liver receives some respite. However, in the clinical appraisal of the individual case, this evidence

20. Pick, F.: Cirrhose du foie d'origine péricardique, Arch. de méd. **2**:105-107 (July) 1896; Ueber chronische unter dem Bilde der Lebercirrhose verlaufende Pericarditis (pericarditische Pseudolebercirrhose) nebst Bemerkungen über die Zuckergussleber (Curschmann), Ztschr. f. klin. Med. **29**:385-410, 1896.

appears to be of limited value, owing to the fact that even under these circumstances the development of true cardiac cirrhosis is uncommon.

SUMMARY AND CONCLUSIONS

The usual histopathologic picture of the liver in cases of prolonged or recurrent episodes of congestive heart failure is that of central lobular atrophy or necrosis or both. Condensation of reticulum and thickening may or may not be present.

The presence of condensation of reticulum alone does not warrant the use of the term cardiac cirrhosis.

True cirrhosis, developing in the course of congestive heart failure, does occur but is rare. No definite criteria were elicited from this study whereby the development or presence of cardiac cirrhosis can be recognized clinically.

ENLARGEMENT OF THE LIVER IN DIABETIC CHILDREN

I. ITS INCIDENCE, ETIOLOGY AND NATURE

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During the past few years we have been impressed with the fact that in children with severe diabetes mellitus which has not been brought under satisfactory control, well marked enlargement of the liver may occur. In this paper we are reporting studies of 60 children (54 living and 6 dead) with pronounced hepatomegaly from among 1,077 patients (815 living and 262 dead) in whom the onset of diabetes occurred at the age of 15 years or under; the list as here presented is not complete. In view of the large number of cases we regard enlargement of the liver as one of the outstanding complications of uncontrolled severe juvenile diabetes. The cause of the increase in size, the nature of the enlargement—whether fatty, glycogenous or otherwise—and the specific treatment present difficult and interesting problems.

As Hanssen [1] has pointed out, little mention of gross hepatomegaly in human diabetes is to be found in the literature. He cited Umber [2] and von Noorden and Isaac [3] as referring to this complication. It is true that as early as 1748 Mead [4] called attention to fatty infiltration of the liver in diabetes. Adlersberg and Porges [5] said they considered an enlarged and fatty liver a regular finding. In his text on diabetes

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1. Hanssen, P.: Enlargement of the Liver in Diabetes Mellitus, J. A. M. A. **106**:914 (March 14) 1936.

2. Umber, F.: Ernährung und Stoffwechselkrankheiten, ed. 3, Berlin, Urban & Schwarzenberg, 1925.

3. von Noorden, C., and Isaac, S.: Die Zuckerkrankheit und ihre Behandlung, ed. 8, Berlin, Julius Springer, 1927.

4. Mead, R., cited by Widnäs, K.: Etudes sur le diabète sucré chez l'enfant, Uppsala, Almqvist & Wiksells, 1928.

5. Adlersberg, D., and Porges, O.: Zur Theorie und Praxis der kurativen Diabetesbehandlung, Klin. Wchnschr. **5**:1451 (Aug. 6) 1926.

Naunyn [6] stated that "in man one finds, as already described by Klebs, marked fatty infiltration of the liver."

In a monograph published in 1926 Priesel and Wagner [7] stated that they had repeatedly observed enlargement of the liver in children with uncontrolled diabetes. They said they regarded the increase in size as due to fat and found that there was a tendency for the organ to return to normal with improvement in the diabetic condition. In 1932 one of us (P. W.) [8] recorded the fact that at autopsy, fatty infiltration of the liver was present in 7 diabetic children. Furthermore, mention was made of roentgenologic evidence in a living patient (case 14) of a decrease in size of an enlarged (and presumably fatty) liver with institution of careful treatment of the diabetes. The complication has probably escaped general notice in the past because it is encountered chiefly in cases of severe, poorly controlled diabetes. These occur particularly in children, and in the pre-insulin days such patients usually lived for only a few weeks or months and so escaped prolonged observation and study.

A case of the type described in this paper was reported by Mauriac [9] in 1934. His patient was a dwarf with a large abdomen, and in this case a collateral circulation developed in the abdominal wall.

PRESENTATION OF DATA

We have made special studies of 60 patients with well marked enlargement of the liver.[10]

Sex.—Although the patients were not selected with this point in mind, there was an equal number of boys and of girls, 30 each.

Age.—The average age of the 54 living patients was 14.9 years in January 1937. The average age in the 6 fatal cases at death was 18.7 years.

Duration of Diabetes.—The age at which the enlargement of the liver was first noted varied from 4 to 21.1 years, with an average of 11.9 years. On the average, five and seven-tenths years elapsed from the time of the onset of diabetes until the enlargement of the liver was

6. Naunyn, B.: Der Diabetes melitus, ed. 2, Vienna, A. Hölder, 1906, p. 284.

7. Priesel, R., and Wagner, R.: Die Pathologie und Therapie der kindlichen Zuckerkrankheit, Ergebn. d. inn. Med. u. Kinderh. **30**:536, 1926.

8. White, P.: Diabetes in Childhood and Adolescence, Philadelphia, Lea & Febiger, 1932, p. 169.

9. Mauriac, P.: Hépatomégalies de l'enfance avec troubles de la croissance et du métabolisme des glucides, Paris méd. **2**:525 (Dec. 29) 1934.

10. To save space a table (table 1) which presents the data concerning these patients in detail appears only in the reprints.

noted. The average period of observation of the living patients after the discovery of hepatomegaly was three and six-tenths years.

Type of Dietary Treatment.—The great majority of these patients had been supposedly receiving diets with a carbohydrate-fat ratio of 2 : 1. As a matter of fact, many of them had paid scant attention to dietary restrictions, eating irregularly and freely. The cases are therefore, by and large, ones of uncontrolled diabetes.

As an indication of the type of diet now prescribed in such cases, actual average figures for the diets of the boys and girls at a camp during the summer of 1936 (approximately 200 children) are given in the following tabulation:

Age, Yr.	Carbohydrate, Gm.	Protein, Gm.	Fat, Gm.	Calories	Calories per Kg. of Body Weight
0- 5	168	64	72	1,556	82
6-10	196	84	85	1,885	67
11-15	215	98	95	2,107	51
16-20	221	99	88	2,072	38

Severity of Diabetes.—As an index of the severity of the diabetes one may point to the average (highest) blood sugar value during fasting for the group (living patients), 0.38 per cent, and average dosage of insulin, 48 units a day.

Complications.—Nothing attests so convincingly to the severity and the lack of control of the diabetes of these young patients as an enumeration of the diabetic complications found in the group. Of the 54 living patients, 38 had had one or more attacks of severe acidosis or coma; 42 had had frequent attacks of severe hypoglycemia; 26 were true dwarfs, being 4 inches (10 cm.) or more below the standard height for their age; 14 others had infantilism without dwarfism; 9 had arteriosclerosis, as evidenced by sclerosis of the retinal vessels or roentgenologically visible calcification of the arteries of the legs; 1 had cataracts; 7 had had peripheral neuritis; 3 had or had had active tuberculosis, and 15 had had persistent or recurring infections, particularly of the skin or urinary tract. All the 6 children who died had had severe acidosis or coma at some time during their diabetic life, and in 3 instances coma was the primary cause of death. Four of the 6 were true dwarfs; 4 had arteriosclerosis, 1 cataracts, 1 tuberculosis and 2 severe infections other than tuberculosis. One patient died of pulmonary tuberculosis and another of pneumococcic meningitis.

When the statistics were analyzed as to sex, it was apparent that this was not an important factor and that except for abdominal pain and splenomegaly, which occurred almost twice as commonly in the girls as in the boys, the incidence of complications was strikingly similar for the two sexes.

Size of the Liver.—The enlargement of the liver in the cases under discussion was a real factor, not a questionable or transient increase in

size. In most instances the edge of the liver could be felt to descend on inspiration to well below the level of the umbilicus in the mamillary line. By roentgenogram the tip of the liver could be seen to lie in 18 of the 60 cases, at one time or another, in the pelvis and in 3 other cases just at the level of the iliac crest. In many cases the edge of the liver felt firm and hard and it was often tender. The first change noted in the cases in which a decrease in size took place was a softening in consistency, as judged by abdominal palpation. With 1 possible exception no cases of ascites were encountered.

In 31 instances enlargement of the spleen was noted either by palpation or roentgenographically. The roentgenograms showed no enlargement of the kidneys except in 5 cases (cases 12, 14, 56, 57 and 60), but even in those cases the increased size of the shadow was questionable (as in case 57) or slight. In 2 of the 5 cases in which the kidneys were seen post mortem (cases 56 and 60) the size was found to be well within normal limits. In none of the 60 cases was enlargement of the heart demonstrated. Hence one can state that in these children with hepatomegaly, although some enlargement of the spleen took place in about half of them, enlargement of the kidneys or of the heart was not characteristic.

Hepatic Function.—As judged by the usual tests, there was no impairment of hepatic function except in 2 cases: In 1 case (case 10) there was acute catarrhal jaundice, with a plasma bilirubin value as high as 5.6 mg. per hundred cubic centimeters in January 1937; in the other case (case 21) the patient was acutely ill with diabetic coma and hepatitis with jaundice in May 1936. Aside from these 2 cases, determinations of the plasma bilirubin content in 8 other cases yielded values uniformly within a normal range, with figures varying from a trace to 0.3 mg. per hundred cubic centimeters. (In case 25 a value of 0.8 mg. was obtained on one occasion.) Our data in this respect are inadequate and in view of the experience of Rabinowitch [11] should be amplified. He reported an average value of 0.86 units for one hundred and thirteen tests carried out on 10 patients. In 6 of our patients on whom the bromsulphalein test was carried out, no delay in the removal of the dye from the blood stream was noted. Furthermore, in only 1 of 30 cases in which complete determinations of free, combined and total cholesterol were made did a significant lowering of the ratio of cholesterol ester to total cholesterol occur (table 1). Accordingly, although in this condition there is undoubtedly some impairment of hepatic function as regards carbohydrate and fat metabolism, the tests available were

11. Rabinowitch, I. M.: Effects of Betaine upon the Cholesterol and Bilirubin Contents of Blood Plasma in Diabetes Mellitus, Canad. M. A. J. **34**:637 (June) 1936.

inadequate to demonstrate this probable diminution in function in the patients studied.

Signs and Symptoms.—Because of the huge size of the liver, in most of these children (44 of 60) the abdomen was large and protuberant. The general effect was heightened in many cases by the fact that the children were underheight, 30 of the 60 being diabetic dwarfs. Bouts of abdominal pain were of relatively frequent occurrence, having been noted in 55 per cent of the group under discussion. This was at times so severe as to lead to a surgical consultation, because of the possibility of an acute intra-abdominal surgical condition. Indeed in case 15 of the series the patient, while in a neighboring hospital, was operated on for acute disease of the gallbladder because of just such an attack of pain accompanied by mild fever and leukocytosis. At operation no abnormality of the gallbladder was made out. The enormous size of the liver was verified, but unfortunately no biopsy was made. One other patient (case 9) was operated on at the New England Deaconess Hospital because of abdominal pain, but only the enlarged liver and calcified lymph nodes were evident. Still another patient (case 21) was admitted to the hospital in diabetic coma with marked abdominal pain, fever and jaundice. He was very ill for several days, with the signs and symptoms of hepatitis, but gradually improved and is alive and reasonably well today. This case has been reported elsewhere.[12]

We have attributed the abdominal pain in many of these cases to stretching of the hepatic capsule and of the accompanying visceral peritoneum.

Hematologic Findings.—Enumerations of the erythrocytes and of the leukocytes, together with the determination of the hemoglobin values and (in some instances) studies of stained blood smears, were made almost as a routine. Since no significant abnormalities were evident, these data are not reported in detail.

Gastric Acidity.—In 8 cases gastric analyses were carried out, an alcohol test meal (and in some instances, also histamine) being used. In 2 cases (cases 12 and 25) no free hydrochloric acid was found. Further observations need to be made to warrant conclusions.

Analyses of Duodenal Contents.—Through the courtesy and cooperation of the late Dr. Lee MacPhee and of Miss Alison T. Fernald, formerly of the Evans Memorial Hospital, we were able to make analyses of the duodenal contents of 7 of the patients. The procedure used was as follows:

12. Root, H. F.: Diabetic Coma and Acute Pancreatitis with Fatty Livers [case 5], J. A. M. A. **108**:777 (March 6) 1937.

A duodenal tube was passed and its position checked roentgenographically. After the duodenal contents during fasting had been obtained, a fat meal, consisting of 5 cc. of oleic acid, followed by 25 cc. of warm water, was introduced through the tube. After a rest period of fifteen minutes, during which the tube was shut off, the clamp was released and the tube allowed to clean itself of oleic acid. Then, collection of B bile was begun and carried out until a definite and marked change in color occurred in the material secured. At this point the collecting flask was replaced by another and the collection continued. The latter material was designated C bile. Analyses of the enzyme content were carried out on samples of C bile as well as on those of B bile according to the methods devised by McClure.[13]

The results of the analyses are given in table 2. Because of his large experience in this field, the results were shown to Dr. C. W. McClure, who made the following statement: "The figures are sufficiently abnormal to denote mild to well marked functional disturbance in the external pancreatic functions of enzyme secretion."

TABLE 2.—*Analyses of Duodenal Contents*

Characteristics	Low Normal Values	Case Numbers						
		15	37	36	33	30	28	20
B Bile								
Volume, cc.	...	120	28	8	22	75	25	14
Time for collection, min.	...	100	25	7	25	16	10	14
Amylolytic activity	1.0	1.8	2.2	1.1	0.5	0.6	0.6	0.7
Proteolytic activity	2.0	2.2	2.3	1.1	1.0	1.0	1.1	0.7
Lipolytic activity	1.0	1.6	0.7	0.9	...	1.4	2.1	1.1
C Bile								
Volume, cc.	...	...	51	...	11	17	55	20
Time for collection, min.	...	...	12	...	15	30	15	30
Amylolytic activity	2.0	...	0.0	...	0.3	0.5	0.0	0.0
Proteolytic activity	2.0	...	0.8	...	1.0	1.0	0.6	0.3
Lipolytic activity	1.0	...	0.1	...	1.0	1.3	0.0	0.0

COMMENT

Our assumption has been that the enlargement of the liver in these cases is due primarily to extensive infiltration and deposition of fat. There are those, however, who have attributed it to marked deposition of glycogen somewhat similar to that found in von Gierke's disease. There is something to be said in favor of this view. This is outweighed in our opinion by the evidence—admittedly indirect—that the large liver is primarily filled with fat, and in the following paragraphs this evidence will be presented. We do not deny that the liver is probably also

13. McClure, C. W.; Wetmore, A. S., and Reynolds, L.: New Methods for Estimating the Enzymatic Activities of Duodenal Contents of Normal Man, Arch. Int. Med. **27**:706 (June) 1921. McClure, C. W.; Mendenhall, W. L., and Huntsinger, M. E.: Studies in Liver Function: IV. A Procedure for the Uniform Stimulation of the Biliary Flow, Boston M. & S. J. **193**:1052 (Dec. 3) 1925. McClure, C. W.: Functional Activities of the Pancreas and Liver, New York, Medical Authors' Publishing Company, 1937.

well filled with glycogen; indeed, our experience suggests that this is true.

Postmortem Data.—To find records of postmortem data for juvenile diabetic patients with marked hepatomegaly is more difficult than one would anticipate. In 4 of our 6 fatal cases an autopsy was performed. Unfortunately the interpretation of the findings was made difficult in 2 of the cases because of marked accompanying infection which in itself may cause fatty changes in the liver. The data as regards the liver in these cases are as follows:

CASE 55.—A boy aged 16 years, who weighed 66 pounds (30 Kg.) when dressed, died in diabetic coma. Microscopic examination showed fine vacuoles of fat in the endothelium of the sinusoids. The hepatic cells were vacuolated.

CASE 56.—A woman aged 23.6 years, who weighed 92 pounds (42 Kg.), died of pneumococcic meningitis. The liver weighed 1,900 Gm. It was light reddish brown and mottled with yellow. The capsule was smooth. On section the liver was soft and friable, with yellowish mottling; and the cut surface was greasy. The gallbladder was normal and contained approximately 80 cc. of thin, golden-brown bile. The bile ducts were patent. Microscopic study showed fine vacuolation of many of the hepatic cells. The periportal nuclei were vacuolated.

CASE 58.—A boy aged 14.8 years, who weighed 40 pounds (18 Kg.), died of extensive pulmonary tuberculosis. The liver weighed 1,520 Gm. The surface was brownish and mottled with reddish foci. On section the edges everted slightly. The cut surface was yellowish brown, showed slight congestion around the central vein and was markedly greasy. The gallbladder was normal, and the bile ducts were patent. There were no stones. Microscopic examination showed extensive fatty and glycogenic infiltration. There was marked congestion around the central vein. Round cell infiltration of periportal spaces was noted. There were foci of necrosis with Langhans' giant cells.

CASE 59.—A girl aged 16.8 years, who weighed 106½ pounds (48 Kg.), died in diabetic coma. The liver seemed rather large and weighed 1,980 Gm. It was yellowish but mottled with red spots and stripes. On section it was uniformly yellowish, with little more than a suggestion of red stripes around the lobules. A yellowish nodule was seen in the parenchyma. Microscopically the hepatic cells showed marked fatty and granular degeneration. Many of the nuclei were large and hyalinized, giving the picture usually produced by glycogenic degeneration.[14]

Aside from the data in these 4 cases, we have been able to collect little information regarding pathologic observations in the disorder under discussion. Until the recent publication of the paper by Brian, Schechter and Persons,[15] we had found no report in the literature, and no pathologist with whom we had spoken or corresponded

14. The data were furnished by the New York Hospital. Further details of the postmortem observations are given in another report (Ralli, E. P., and Waterhouse, A. M.: Diabetic Coma Occurring Nineteen Times in the Life of a Patient with Diabetes Mellitus, J. Lab. & Clin. Med. **18**:1119 [Aug.] 1933).

15. Brian, E. W.; Schechter, A. J., and Persons, E. L.: Unusual Glycogen Storage in a Case of Diabetes Mellitus, Arch. Int. Med. **59**:685 (April) 1937.

had had a suitable record in his files. It is generally conceded, as already mentioned, that fatty infiltration of the liver may be found in diabetic patients at autopsy, but it is difficult to find published reports of cases in which the subject was a diabetic child with hepatomegaly (without complications such as infections).

The case reported by Brian, Schechter and Persons was that of a 24 year old man with poorly controlled diabetes of over four years' duration who died in severe acidosis. At the postmortem examination the liver was large (weight, 2,700 Gm.), and "the cut surface was waxy yellow and swollen." From a microscopic study of stained sections and from the fact that after eighteen months' storage in an aqueous preserving fluid (containing a dilute solution of formaldehyde U. S. P. 1:100) the glycogen content of the liver was found to be 3.18 per cent, Brian and his associates concluded that the hepatomegaly in their patient was due chiefly to glycogen. Chemical analyses carried out recently in our own laboratory on a portion of this liver (sent to us by Dr. W. D. Forbus, of the department of pathology of Duke University) gave a value for total lipid of 8.95 Gm. per hundred grams of dried hepatic substance (calculated as oleic acid). Although one may well question the validity of such a determination, made after the specimen had been in a preserving fluid for months, a figure as low as this supports the contention of Brian, Schechter and Persons that in their patient the enlargement of the liver was not due to fat. It is only fair to state, however, that review of the microscopic sections in this case by Dr. Shields Warren, of the department of pathology of the Harvard Medical School, suggested that in the enlargement hydropic degeneration may have played a large part.

Biopsies.—Abdominal exploration with biopsy of the liver has not been carried out for any of our patients. No report in the literature has come to our attention except the recent one of Stetson and Ohler.[16] Their patient was a 12 year old boy with diabetes, enlargement of the liver and spleen, ascites, jaundice and mild fever. There was, therefore, definite hepatitis, and the situation was not strictly comparable to that in the cases reported in this paper. It is important to note, however, the statement of Stetson and Ohler that "microscopic examination of a section of this tissue (removed at biopsy) stained with Best's carmine showed essentially normal liver structure with a tremendous amount of intracellular glycogen. The nuclei contained no glycogen, and there were but small amounts scattered about in the connective tissue." No signs of increase in fat deposits were seen. No chemical analyses for glycogen or fat were made.

16. Stetson, R. P., and Ohler, W. R.: Hepatomegaly and Jaundice in a Juvenile Diabetic, New England J. Med. **217**:627 (Oct. 14) 1937.

Analogy from Depancreatized Dogs.—Investigators have long observed that in totally depancreatized dogs the liver is likely to become large and filled with fat. Thus Naunyn,[17] in 1906, wrote as follows:

In scarcely a single dog among the great number which I have seen die of severe diabetes following complete extirpation of the pancreas have I missed marked fatty infiltration of the liver; among these animals were many without infection, to which Sandmeyer said he was inclined to attribute it. . . . Such livers can be compared macroscopically with those in the most severe cases of

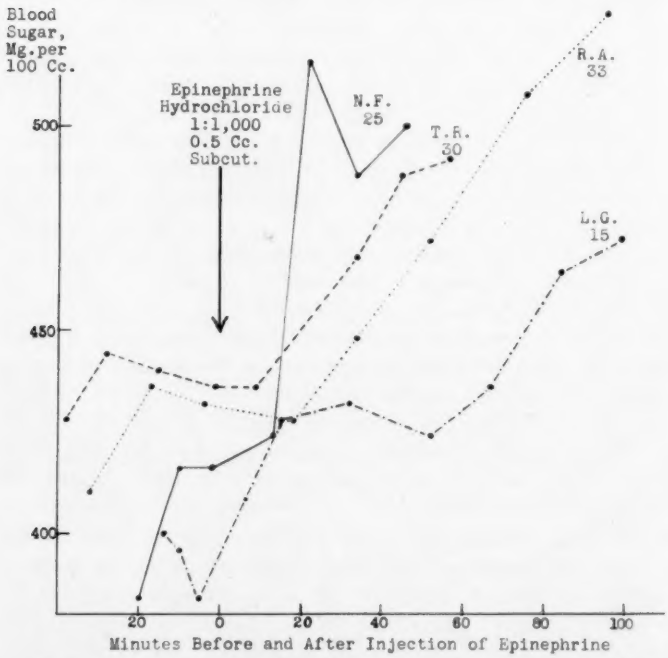

Chart showing blood sugar (capillary) curves obtained after the subcutaneous administration of 0.5 cc. of epinephrine hydrochloride (1 : 1,000) subcutaneously. The results for 3 other patients (cases 5, 7 and 28) were essentially the same. All the patients were resting in bed throughout the making of the tests and had received no food or insulin for ten hours. In 5 of the 7 cases control tests were carried out on other days with conditions exactly the same except that no epinephrine was given. These control curves in no instance showed a rise in blood sugar content exceeding 28 mg. per hundred cubic centimeters over the period covered by the experiment.

acute phosphorus poisoning in man or with the livers of fattened geese—so large, so bright yellow and so friable are they. The microscope shows the cells to be

17. Naunyn,[6] p. 118.

remarkably filled with fat. . . . The weight of the liver is enormous; I found livers weighing over 1 Kg. in dogs of approximately 10 Kg.

The characteristic observation so vividly described by Naunyn is a strong argument in favor of the contention that the hepatomegaly in juvenile diabetes is primarily due to fat.

As will be discussed in detail in our next paper, this fatty enlargement of the liver in depancreatized dogs does not occur if sufficient insulin is given to control the diabetes and if raw pancreas, lecithin or choline is added to the diet.[18]

Differences from von Gierke's Disease.—It is characteristic of glycogen storage (von Gierke's) disease that the persons affected exhibit little or no rise in blood sugar content after the injection of epinephrine and are extremely sensitive to insulin. Our patients showed normal responses to epinephrine hydrochloride (four typical curves are shown in the occompanying chart) and were no more sensitive to insulin than is the average child with severe diabetes.

Furthermore, one thinks of an excess of stored glycogen as occurring with an excess of insulin in the body. In our cases of diabetes with hepatomegaly, a gross lack of insulin was characteristic.

Coexistence of Glycogen and Fat in the Liver.—It must be remembered that large amounts of glycogen and fat may coexist in the liver. The presence of a large amount of fat in the liver of the diabetic child does not preclude the presence of an amount of glycogen which approaches the normal. Thus in cases of glycogen storage (von Gierke's) disease, Krakower[19] observed marked fatty infiltration accompanying the abnormal deposit of glycogen.

CONCLUSION

Our chief purpose in this paper has been to present the clinical and laboratory findings for a sizable group of diabetic children with hepatomegaly. In the discussion we have, in general, supported the view that the primary cause of the enlargement of the liver is usually the deposition of fat rather than that of glycogen. We freely admit that the evidence is largely indirect and not supported by the observations in 2 cases reported by others, 1 at autopsy[15] and 1 at biopsy,[16] which most nearly resemble those presented here. We still hold to the belief, however, that fat is more reprehensible in this connection than is glycogen. We consider it possible that, in addition, a large role may be played by degenerative changes in the hepatic cells leading to imbibition of

18. Best, C. H.: The Role of the Liver in the Metabolism of Carbohydrate and Fat: III. The Deposition of Liver Fat, Lancet **1**:1274 (June 16) 1934.

19. Krakower, C.: The Lipoid Factor in Glycogen Storage Disease, J. Pediat. **9**:728 (Dec.) 1936.

fluid and hydropic swelling. This is supported by Warren's interpretation (referred to previously) of the tissue from the patient reported on by Brian, Schechter and Persons.[15] Warren has pointed out also that the frequent occurrence of abdominal pain in these children is a point in favor of an acute swelling, which might take place more quickly from hydropic degeneration with retention of water than from deposition of fat. Kaplan and Chaikoff [20] have shown that a measurable amount of water does not accompany the storage of either glycogen or fat in the liver. In our own cases, possibly a primary deposition of fat was followed by hydropic degeneration with rapid retention of water, causing stretching of the hepatic capsule and acute pain.

Fortunately the problem is not insoluble. One needs only careful histologic and chemical studies of the liver in a sufficient number of suitable cases. We hope that the present report may stimulate interest in the subject so that collection of such data may be furthered. In this connection it is well to call attention to the undesirability of drawing too definite conclusions from small slices of liver obtained at biopsy, since there may be a great deal of variation between one area and another.[21]

SUMMARY

Attention is called to gross enlargement of the liver in children with severe, poorly controlled diabetes, and detailed findings in 60 cases are presented. An enlarged spleen was noted in 31 cases.

The series is noteworthy for the frequency of complications, including diabetic coma and acidosis, hypoglycemic attacks, dwarfism, arteriosclerosis, neuritis, tuberculosis and other infections, chiefly of the skin and urinary tract.

Dwarfism, a protuberant abdomen and bouts of abdominal pain were particularly striking features.

Evidence is presented to support the view that the enlargement in such cases is primarily due to gross fatty infiltration. The condition is considered as one apart from glycogen storage disease, although the presence of glycogen in amounts approaching the normal is not denied. The possible role of hydropic degeneration with retention of water is discussed.

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20. Kaplan, A., and Chaikoff, I. L.: The Relation of Glycogen, Fat and Protein to Water Storage in the Liver, J. Biol. Chem. **116**:663 (Dec.) 1936.

21. Chaikoff, I. L., and Kaplan, A.: The Distribution of Fat in the Livers of Depancreatized Dogs Maintained with Insulin, J. Biol. Chem. **119**:423 (July) 1937.

ENLARGEMENT OF THE LIVER IN DIABETIC CHILDREN

II. EFFECT OF RAW PANCREAS, BETAINE HYDROCHLORIDE AND PROTAMINE INSULIN

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In the preceding paper we [1] discussed the general characteristics of hepatomegaly as seen in 60 diabetic children possessing this complication. The present report is concerned with the results of treatment with three agents; raw pancreas, betaine hydrochloride and protamine insulin.

METHODS

All the children were kept under close observation, and most of them spent one or more weeks in the hospital during the period of study. For the greater part of the time, however, the patients were at home, because of the expense and undesirability of prolonged hospitalization. One must accept the fact that the care taken by the patients and their families as regards diet and insulin probably varied somewhat from time to time, so that strictly comparable conditions throughout cannot be claimed. It is most likely that during the periods of special medication, as with betaine and with protamine insulin, more care was given also to other details of treatment, thus favoring better general control of the diabetic condition.

At first roentgenographic examinations of the abdomen regarding the size of the liver were made at frequent intervals—as often as every week, but in the study of the patients taking betaine it soon became apparent that changes would take place only over longer periods. Hence, roentgenographic studies were made only at intervals of three or more months. (Later experience with protamine insulin showed, however, that changes in size might occur in a much shorter length of time.) All the roentgenograms were taken in the same laboratory

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1. Marble, A.; White, P.; Bogan, I. K., and Smith, R. M.: Enlargement of the Liver in Diabetic Children: I. Its Incidence, Etiology and Nature, Arch. Int. Med., this issue, p. 740.

under standard conditions, and all the measurements were made by the same roentgenologist (I. K. B.). In order to obtain values of as great accuracy as possible, the following precautions were observed: 1. The same target-film distance was used in all cases. 2. Care was taken to place the apparatus and the patient so as to allow the central ray to pass through a fixed measured point on the anterior abdominal wall. 3. The exposure was made always at the end of a full inspiration.

In establishing the size of the liver three measurements were taken: (1) the vertical diameter; (2) the long diameter, from the tip of the right lobe to the most distant point along the upper margin, and (3) the angle made by the tip of the right lobe. The liver was considered (1) unchanged in size if the variations of the vertical and long diameters were under 1 cm. and if the change in the angle was less than 5 degrees; (2) slightly increased or decreased in size if the variations of the vertical and long diameters were from 1 to 1.9 cm. and if the change in the angle was between 6 and 10 degrees; (3) moderately increased or decreased in size if the variations in the vertical and long diameters were from 2 to 2.9 cm. and if the change in the angle was between 11 and 15 degrees, and (4) markedly increased or decreased in size if the variations in the vertical and long diameter were 3 cm. or over and if the change in the angle was more than 15 degrees.

For the studies of lipids, blood was withdrawn whenever possible with the patient in the fasting state. Potassium oxalate was used as an anticoagulant. The plasma was separated and the alcohol-ether extract made as soon as possible after the withdrawal of the blood, in most cases in less than two hours. The total cholesterol value was determined by the method of Bloor,[2] and free and ester cholesterol values were determined by the procedure suggested by Smith and Marble.[3]

The betaine hydrochloride used was chemically pure and was prepared especially and furnished without cost by Merck & Co., Inc.

RESULTS

(*a*) *Raw Pancreas.*—Two patients, a boy of 13 years (case 30) and a girl of 19 years (case 15), were noted to have enormous enlargement of the liver. The diabetes, which in the first case was of over nine years' and in the second of over six years' duration, had in each instance been continuously poorly controlled. For a period of ten to eleven weeks each patient was given 120 to 125 Gm. of finely ground, fresh, raw pancreas daily, usually in cold tomato juice. Frequent physical and roentgenologic examinations showed no diminution in the size of the liver. As may be seen from table 1, no significant change was produced in the level of blood cholesterol or in the percentage of the ester

2. Bloor, W. R.: The Determination of Small Amounts of Lipid in Blood Plasma, J. Biol. Chem. **77**:53 (April) 1928.

3. Smith, R. M., and Marble, A.: The Colorimetric Determination of Free and Combined Cholesterol, J. Biol. Chem. **117**:673 (Feb.) 1937.

fraction. Because of the essentially negative character of these results and the distastefulness of the raw pancreas, this form of experimental therapy was given up, and attention was directed to betaine.

(*b*) *Betaine Hydrochloride.*—Twelve children were given betaine hydrochloride over a period of from eight to nineteen months, usually 3 Gm. daily. Seven of these patients cooperated well and took the betaine as prescribed; the other 5 took it irregularly. For part of the period the betaine was mixed with the food, and for part it was administered in capsules. No difference was noted in the results secured. To a control group of 6 children with similar enlargement of the liver no betaine was given. In tables 2 and 3 the results obtained are summarized (see also the general summary given in table 5).

TABLE 1.—*Effect of Raw Pancreas on the Cholesterol Content of the Blood in Two Cases*

	Cholesterol				
Date, 1935	Free, Mg. per 100 Cc.	Ester, Mg. per 100 Cc.	Total, Mg. per 100 Cc.	Ester in Total, Percentage	Comment
Master T. R. (case 30)					
March 17	68	170	238	71	125 Gm. of raw pancreas daily from Feb. 28, to May 10, 1935
April 11	64	135	202	69	
May 14	83	164	246	66	
July 15	85	143	228	63	
Miss L. G. (case 15)					
March 6	..	...	225	..	120 Gm. of raw pancreas daily from March 12, to at least June 7, 1935
April 9	65	156	211	69	
August 5	63	156	219	71	

It will be noted that whereas only 1 of the 6 patients in the control group showed a diminution in the size of the liver during the period of special study, 6, or 50 per cent, of those receiving betaine showed such a decrease. Thus there seems to have been some effect attributable to the betaine. As we followed the studies closely, however, we were not impressed by any sudden or dramatic decrease in the size of the liver. Such effect as was secured did not impress us as a definite response to a specific remedial agent. Moreover, it is entirely possible that some of the beneficial results seen in the patients taking betaine was due to the fact that greater care was taken by them as regards diet and insulin, because of the common experience that whenever a special type of treatment is introduced there is often greater attention to other details.

There was little or no effect on the plasma cholesterol, free, ester or total, as may be seen in table 2.

TABLE 2.—*Effect of the Oral Administration of Betaine Hydrochloride on the Size of the Liver and the Plasma Cholesterol Content* *

Case No., Sex	Age on Jan. 1, 1937	Severity of Diabetes: Duration of Diabetes to Jan. 1, 1937	Severity of Diabetes: Highest Fasting Blood Sugar Value, %	Severity of Diabetes: Usual Daily Dose of Insulin Units	Administration of Betaine: Date Started	Administration of Betaine: Date Stopped	Size of Liver†: Date	Upper Border	Lower Border, Cm.	Angle, Degrees	Long Diameter, Cm.	9th Thoracic Vertebra to Sacrum, Cm.	Body Width, Cm.	Interspinal Diameter, Cm.	Summary of Results	Plasma Cholesterol: Date	Total, Mg. per 100 Cc.	Free, Mg. per 100 Cc.	Ester, Mg. per 100 Cc.	Ester, % of Total
I. Betaine Taken Regularly (7 Cases)																				
7 F	20.8	13.1	0.47	52	February 1936	September 1937	2/29/36	...	+2.6	..	....	....	34	....		2/29/36	212	50	156	76
							6/16/36	...	+1.0	62	....	19.0	34.5	....		3/31/36	231	57	166	75
							9/21/36	6+	+3.9	60	29.6	19.0	34	....						
							1/20/37	6+	+5.5	60	29.0	....	....	....	No change					
30 M	15.8	11.6	0.55	76	July 1935	March 1936	5/11/35	8+	+0.5	70	....	22.2	27.3	20.8		7/15/35	228	85	143	63
							12/11/35	7	+2.0	..	24.0	22.4	30.7	23.3		10/18/35	410	104	306	74
							3/ 4/36	8	+3.2	62	21.5	23.5	29.8	23.0	Slight decrease	12/ 7/35	220	58	162	73
																3/ 7/36	213	55	158	74
31 F	14.9	8.4	0.49	52	July 1935	March 1936	7/ 1/35	7+	—3.4	55	26.4	20.3	26.0	21.4		7/10/35	269	76	193	71
							12/21/35	7	—1.5	53	27.5	21.7	28.7	24		11/27/35	234	70	164	70
							7/27/36	7	—3.0	53	29.2	22.3	27.5	25.2	Slight increase	12/28/35	235	66	168	72
32 M	18.2	8.5	0.23	60	July 1935	March 1936	7/ 9/35	...	+2.6	55	....	20.8	....	24.5		7/15/35	240	69	162	71
							10/ 5/35	7	+1.0	50	23.7	22.2	28.7	24.8		12/ 7/35	156	38	114	76
							12/11/35	...	+4.1	45	....	22.3	29.0	24.8		1/ 4/36	151	39	109	74
							3/14/36	6+	+5.9	47	22.9	22.9	29.7	25.5	Slight decrease	2/ 1/36	139	38	99	73
37 F	16.4	10.0	0.44	64	July 1935	March 1936	7/27/35	6+	+3.0	55	24.5	21.1	27.8	21.6		8/ 3/35	281	68	205	76
							10/22/35	7	+1.5	51	25.7	21.5	28.8	22.3		8/ 6/35	240	70	168	71
															No change	10/19/35	328	88	237	76
39 F	15.5	11.6	0.44	52	April 1935	March 1936	4/ 6/35	8	+1	57	....	22.2	26.7	24.2		4/ 8/35	271	63	209	77
							10/19/35	9	+3.8	58	....	23.5	28.4	26.1		7/19/35	235	65	169	72
							12/14/35	...	+6.3	53	....	24.0	29.0	26.1		10/16/35	239	59	178	76
							7/ 9/36	7	+8.9	35	21.4	23.5	28.4	26.0	Marked decrease	11/16/35	244	64	166	74
																1/11/36	226	66	160	71

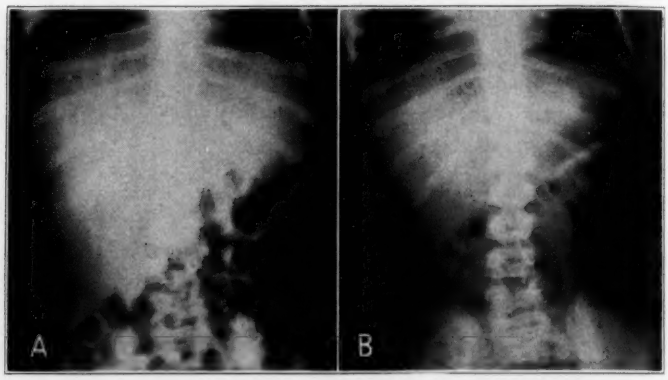
36 F	17.5	6.3	0.30	70	July 1935	March 1936	12/11/35 3/14/36	9 9	+2.5 +2.0	50 50	24.8 25.0	25.5 26.1	28.4 29.3	27.2	No change	8/ 3/35 12/ 7/35 1/ 4/36 3/ 7/36	234 228 212 159	61 71 65 47	165 157 147 112	74 69 69 70
II. Betaine Taken Irregularly (5 Cases)																			
11 M	14.8	12.4	0.42	62	March 1935	March 1936	3/25/35 7/20/36	7 7	−2.4 +0.6	48 53	25.3	20.8 22.7	28.5 29.4	22 23.7	Moderate decrease	3/ 6/35 6/20/35	192 190	50 ..	142	74 ..
20 M	13.1	7.8	0.48	34	July 1935	March 1936	4/13/35 1/25/36 3/25/36 7/30/36	8 ... 7+ 8	−2.1 −1.6 −1.4 −1.8	63 58 60 60	24.8 .... 25.5 25.0	21.0 22.2 22.2 22.3	28.0 29.2 29.7 28.7	23 24.4 25.0 24.8	No change	7/12/35 9/ 3/35 10/24/35 1/25/36	166 173 142 160	.. 41 36 44	.... 132 107 116	.. 76 75 72
25 M	15.9	6.9	0.42	69	February‡ 1935	March 1936	2/ 8/35 5/11/35 1/25/36	... 9+ 8+	−2.3 −3.2 −4.6	54 45 52	.... 30.7+	23.7 23.8 25.7	.... 27.8 35	26.0 27.0 29.5	Moderate increase	3/23/35 4/13/35 10/26/35 1/25/36	178 162 151 215	51 53 59 55	118 107 96 158	71 67 61 74
33 M	14.9	8.5	0.47	56	July 1935	March 1936	3/12/35 5/28/35 12/20/35 3/30/36 7/30/36	7 ... 8+ 8 8	+1.0 +1.1 +0.7 +1.3 +1.7	55 .. 55 .. 53	.... 23.7 24.0 24.0	21.5 21.4 22.5 23.0 22.8	28.3 28.5 29.8 30.8 29.7	22.3 23.2 24.0 24.3 24.2	Slight decrease	7/12/35 10/26/35 1/11/36 1/25/36 3/30/36	144 204 176 160 136	.. 59 47 43 41	95 145 129 113 92	66 71 73 73 70
49 M	14.1	3.6	0.21	32	July 1935	March 1936	4/22/35 10/26/35 7/22/36	8— ... 8—	+1.5 +2.1 +5	46 47 48	21.0 .... 18.3	21.4 .... 23.0	28.5 29.0 28.7	23.5 24.5 24.7	Moderate decrease	10/26/35	239	64	166	73

* The daily dose of betaine hydrochloride was 3 Gm. All the observations were made before the institution of treatment with protamine insulin.

† In tables 2 to 4 the values for the size of the liver represent measurements made of roentgenograms as follows: (1) the upper border (the figures given indicate the dorsal vertebra coinciding with the upper margin of the liver, a plus sign indicating the lower margin of the vertebra, a minus sign the upper margin and no sign the midpoint); (2) lower border—centimeters above or below the iliac crest; (3) the angle of the lower tip; (4) the long diameter—the longest straight line measurement from the upper margin to the tip; (5) from the ninth thoracic vertebra to the sacrum—the distance from the lower margin of the ninth thoracic vertebra to the upper margin of the sacrum; (6) the width of the patient's body measured between the inner margins of the ninth ribs at their widest curve, and (7) the interspinal diameter—the distance between the anterior superior spines of the ilia. The last three values are included to indicate the relative sizes of the patient at the various times that the roentgenograms were made.

‡ 1.5 Gm. daily.

(*c*) *Protamine Insulin.*—The use of protamine insulin was begun in this clinic in August 1935 and has been steadily extended. As patients have returned to the hospital for "check-up" they have been shifted to the new preparation, and almost all have continued its use at home. A general summary of the results obtained in the first 1,250 patients has already been published.[4] Of the children discussed in the present paper, all but 1 are now taking protamine zinc insulin (data concerning the control series and those receiving betaine were collected before the use of protamine insulin was begun). Because of the report by Hanssen,[5] we watched this group carefully to detect any change in hepatic size.



Roentgenograms of the abdomen in case 41. *A* was taken on July 27, 1936, when treatment with protamine zinc insulin was begun. *B* was taken on September 12, and shows the marked decrease in the size of the liver.

In 19 instances serial examinations were made by roentgenogram. The results in these few cases are presented in table 4. It can be readily seen that concomitant with the use of protamine insulin, there occurred a diminution in the size of the liver in 15, or 78.9 per cent, of the 19 cases. Our impression is that the decrease in size may begin within two weeks after the institution of such therapy, provided this is done under conditions which allow careful dietary regulation and good control of the diabetes.

Less detailed clinical study of other patients by means of physical examination bears out this finding, namely, that with the better control

4. Joslin, E. P.: Protamine Insulin, J. A. M. A. **109**:497 (Aug. 14) 1937.

5. Hanssen, P.: Enlargement of the Liver in Diabetes Mellitus, J. A. M. A. **106**:914 (March 14) 1936.

TABLE 3.—*Control Series* *

Case No.	Sex	Age on Jan. 1, 1937	Duration of Diabetes to Jan. 1, 1937	Severity of Diabetes: Highest Fasting Blood Sugar Value, %	Severity of Diabetes: Usual Daily Dose of Insulin Units	Size of Liver: Date	Upper Border	Lower Border, Cm.	Angle, Degrees	Long Diameter, Cm.	9th Thoracic Vertebra to Sacrum, Cm.	Body Width, Cm.	Interspinal Diameter, Cm.	Summary of Results	Plasma Cholesterol: Date	Total, Mg. per 100 Cc.	Free, Mg. per 100 Cc.	Ester, Mg. per 100 Cc.	Ester, % of Total
17	M	17.9	9.5	0.29	76	7/ 9/35	8—	+2.0	65	....	21.2	28.3	26.5		4/ 9/35	186	51	135	73
						12/31/35	8—	+1.7	65	....	22.2	30.0	26.5		11/ 9/35	239	69	170	71
															12/28/35	185	62	123	67
														No change	3/ 7/36	230	64	166	72
18	F	16.5	8.8	0.50	30	12/28/35	8+	—3.5	90	27.5	22.5	29.0	25.0						
						8/21/36	8	—1.8	85	27.2	22.6	29.2	25.0	No change					
24	M	13.1	7.0	0.36	48	7/ 9/35	6+	0.0	52	22.5	18.4	26.7	21.5	Slight					
						12/28/35	8	—1.1	..	22.5	19.8	26.5	22.7	decrease					
61	M	8.5	6.9	0.36	40	1/ 4/36	7+	+5.2	60	17.5	19.0	25.0	19.5						
						7/23/36	8	+4.4	50	17.5	19.5	24.1	19.5	No change					
28	M	13.3	9.8	0.30	24	4/23/35	6±	—0.4	56	....	19.8	27.3	19.3		4/24/35	215	55	166	74
						10/ 5/35	7+	+1.0	56	25.0	20.5	27.8	20.3	Slight	10/ 5/35	227	54	181	76
						12/ 7/35	7+	—3.0	67	26.5	20.6	28.0	20.7	increase	11/ 9/35	235	60	183	74
															12/ 7/35	185	57	124	69
35	F	16.8	14.5	0.25	68	7/ 5/35	...	+5.5	73	....	22.2	29.2	24.0		7/ 3/35	283	71	211	75
						12/28/35	7—	+7.5	57	....	23.2	29.6	26.0	No change	10/ 7/35	250	72	181	71
															12/28/35	186	59	127	68

* These observations were made before the institution of treatment with protamine insulin (except in case 18; treatment was begun on Aug. 18, 1936, three days before the roentgenogram was taken).

TABLE 4.—*Effect of Treatment with Protamine Insulin on the Size of the Liver in Nineteen Cases*

Case No.	Sex	Age on Jan. 1, 1937	Duration of Diabetes on Jan. 1, 1937	Highest Fasting Blood Sugar Value, %	Protamine Insulin		Size of Liver								Summary of Results
					Date Started	Dosage, 1937	Date	Upper Border	Lower Border, Cm.	Angle, Degrees	Long Diameter, Cm.	9th Thoracic Vertebra to Sacrum, Cm.	Body Width, Cm.	Interspinal Diameter, Cm.	
5	F	23.3	16.4	0.51	January 1937	50*	7/ 1/35	6+	+0.7	60	25.0	22.0	30.0	25.4	
							10/27/37	7	+4.3	..	23.0	22.5	29.3	....	Moderate decrease
6	M	14.7	12.8	0.55	July 1936	36 + 48*	12/ 7/35	...	+3.5	53	....	23.5	29.5	23.3	
							7/30/36	7	+5.8	52	24.3	24.3	29.5	24.0	
							11/ 6/37	8	+5.8	53	23.8	26.3	31.0	....	Slight decrease
15	F	21.3	8.8	0.41	January 1936	26 + 80*	12/ 4/35	6+	+4.3	63	....	26.0	33.6	30.3	
							8/14/36	6+	+3.5	63	30.5	26.5	34.4	....	
							2/ 3/37	6+	+5.6	60	28.0	26.4	....	....	Moderate decrease
16	F	13.5	9.3	0.40	August 1937	10 + 40*	8/12/37	7+	—0.8	57	28.0	25.6	29.5	30.0	
							10/13/37	7+	+2.2	58	26.7	25.8	29.5	....	Moderate decrease
20	M	13.1	7.8	0.48	July 1936	18 + 22*	7/30/36	8	—1.8	60	25.0	22.3	28.7	24.8	
							3/26/37	8+	+0.5	60	23.0	22.7	28.5	....	Moderate decrease
24	M	13.1	7.0	0.36	July 1936	2 + 58*	7/24/36	7+	0.0	45	21.8	19.6	26.5	22.2	
							3/ 3/37	8+	+2.4	55	20.0	20.7	26.8	23.5	Moderate decrease
25	M	15.9	6.9	0.42	October 1936	20 + 40*	10/31/36	8+	—3.2	45	29.0	26.2	34.0	....	
							2/ 6/37	8+	—2.0	45	27.2	26.4	30.0	....	Slight decrease
28	M	13.3	9.8	0.30	July 1936	44*	7/24/36	7+	+1.9	63	22.6	20.5	27.2	20.3	
							3/ 3/37	7+	+4.3	65	21.5	20.8	27.2	21.2	Slight decrease
30	M	15.8	11.6	0.55	March 1936	8 + 68*	3/14/36	8	+3.2	62	21.5	23.5	29.8	23.0	
							7/30/36	9	+3.5	55	20.0	23.8	29.4	23.3	
							3/ 3/37	8+	+4.1	55	20.0	25.8	28.8	24.5	Moderate decrease

62	F	16.0	14.6	0.42	August 1936	54*	6/ 8/36	9	+1.3	58	23.8	25.5	29.6	23.7	
							10/24/36	10	+0.3	58	23.5	25.5	30.0	....	
							6/11/37	10+	+2.0	60	23.0	26.5	31.0	26.0	Slight decrease
33	M	14.9	8.5	0.47	July 1936	24 + 40*	9/ 8/36	9+	−2.0	52	23.5	22.6	....	....	
							11/ 2/36	8+	+2.6	50	22.2	23.2	29.8	....	
							4/27/37	9	+0.6	43	25.0	24.2	29.4	25.5	
							9/20/37	8+	+1.6	47	23.6	24.5	30.2	....	No change
36	F	17.5	6.3	0.30	June 1936	50*	12/23/36	8	+3.0	43	26.0	26.7	29.7	....	
							3/ 5/37	8+	+2.2	50	26.5	26.6	30.2	....	
							9/29/37	8+	+1.6	45	26.5	26.7	31.5	....	No change
38	M	5.8	3.6	0.29	February 1937	26*	2/13/37	6+	+1.0	70	22.2	18.8	25.2	20.5	
							7/15/37	6+	+4.5	60	19.0	19.2	24.2	21.0	Marked decrease
40	M	5.6	3.7	0.50	July 1936	16*	7/23/36	8	+2.0	57	18.2	17.4	21.7	18.2	
							10/ 5/37	8+	+0.8	52	18.0	18.6	23.0	19.4	No change
42	F	8.3	3.5	0.27	July 1936	14 + 36*	7/27/36	8	−1.8	63	25.5	21.5	25.3	20.5	
							9/12/36	9	+0.4	53	21.0	21.5	24.7	21.0	Marked decrease
43	F	7.8	3.4	0.44†	June 1936	24*	5/14/36	9	−2.4	55	20.0	17.5	22.4	17.2	
							6/18/36	8+	0.0	57	19.5	17.6	23.0	17.5	
							8/19/36	9	−1.0	60	20.4	19.3	22.2	18.0	
							6/30/37	9	+1.2	50	18.0	19.3	....	19.5	Slight decrease
45	M	15.8	6.0	0.31	July 1936	28 + 42*	7/30/36	7	+0.7	..	27.0	23.2	31.2	27.2	
							7/17/37	9	−1.7	..	27.0	26.0	31.2	28.5	
							10/23/37	8+	−1.3	..	26.5	25.8	....	....	No change
52	M	6.3	0.3	0.25	October 1936	24*	10/31/36	8+	+2.0	45	18.5	18.3	21.4	19.0	
							9/22/37	7+	+5.4	..	17.4	19.3	23.2	20.3	Slight decrease
63	F	9.7	8.2	0.43	May 1937	20 + 56*	5/28/37	6	+1.5	63	22.3	17.1	23.5	17.5	
							6/ 4/37	6	+2.0	..	....	17.0	24.2	17.5	
							7/16/37	5+	+2.6	58	20.2	17.4	24.2	17.5	
							9/22/37	7	+1.8	58	20.3	17.8	24.8	18.0	Moderate decrease

* Protamine insulin. Where two figures appear for the dosage, the first one indicates units of regular insulin.
† Not during fasting.

of the diabetes that is made possible with protamine insulin, the enlargement of the liver is prevented or alleviated. This suggests that in the diabetic patient the hepatic changes are due not to the lack of some substance present in raw pancreas or its derivatives but to the poor control of the diabetes, with the accompanying disordered fat metabolism. This seems reasonable in view of the fact that if insufficient insulin is given to dogs made diabetic by total pancreatectomy, the liver may become enlarged and fatty and even large amounts of raw pancreas or its derivatives given orally will only partly diminish its size. This form of hepatomegaly obviously is due primarily to poor control of the diabetes.

TABLE 5.—*Summary Table of Results as Regards the Size of the Liver*

	Total No. of Cases	Increase		No Change	Decrease			Decrease in Size, % of Total Cases
		Slight	Moderate		Marked	Moderate	Slight	
Control series.....	6	1	..	4	..	..	1	16.6
Betaine								
Taken regularly.....	7	1	..	3	1	..	2	....
Taken irregularly....	5	..	1	1	..	2	1	30.0
Protamine insulin.....	19	..	..	4	2	7	6	78.9

COMMENT

The trial of raw pancreas or betaine for diabetic children with hepatomegaly has its rationale in the fact, established shortly after the discovery of insulin, that although a completely depancreatized dog can be kept alive for as long as eight months with lean beef, cane sugar and insulin, it eventually dies with signs of hepatic failure unless fresh raw pancreas is added to the diet. In animals not given raw pancreas, postmortem examination reveals enlargement and fatty degeneration of the liver.[6] Later Hershey[7] and Hershey and Soskin[8] concluded that lecithin is the effective constituent of raw pancreas. The problem was carried a step further by Best and his associates,[9] who established that

6. Allan, F. N.; Bowie, D. J.; Macleod, J. J. R., and Robinson, W. L.: Behavior of Depancreatized Dogs Kept Alive with Insulin, Brit. J. Exper. Path. **5**:75 (April) 1924.

7. Hershey, J. M.: Substitution of Lecithin for Raw Pancreas in the Diet of the Depancreatized Dog, Am. J. Physiol. **93**:657 (June) 1930.

8. Hershey, J. M., and Soskin, S.: Substitution of Lecithin for Raw Pancreas in the Diet of the Depancreatized Dog, Am. J. Physiol. **98**:74 (Aug.) 1931.

9. (*a*) Best, C. H.; Ferguson, G. C., and Hershey, J. M.: Choline and Liver Fat in Diabetic Dogs, J. Physiol. **79**:94 (July 28) 1933. (*b*) Best. C. H.: The Role of the Liver in the Metabolism of Carbohydrate and Fat: Deposition of Liver Fat, Lancet **1**:1274 (June 16) 1934.

choline is the component of lecithin which is active in this connection. Furthermore, betaine, an oxidation product of choline, also was found to be effective.[10] Accordingly, it seemed reasonable that raw pancreas or betaine might be of use in the treatment of diabetic children with enlargement of the liver.

It is evident from the data which have been presented that although greater or less decrease in size of the liver was seen in 50 per cent of the patients given betaine, the change was not uniformly obtained nor was it usually striking in degree. Certainly some of the results seen must be ascribed to better control of the diabetic condition (with diet and insulin) during the period of administration of betaine. The fact that as good or better results were obtained in the patients who took betaine irregularly, as compared with those who took it regularly, strengthens the belief that the beneficial action was not due wholly to betaine. This lack of specific action may be ascribed to the following factors:

1. Choline is found in many foods[11] and, as far as we can judge, was already present in adequate amount in the diets of the children.

2. Influences other than the lack of choline may well be and probably are the cause of the enlargement of the liver seen in diabetic children. Other factors which Best and his associates have found to possess a lipotropic action are certain dietary proteins[12] and extracts of the anterior lobe of the pituitary gland.[13] The beneficial effect which followed the use of protamine insulin in our patients suggests that in them uncontrolled diabetes per se was the fundamental cause of the hepatomegaly.

3. There is a decided difference between depancreatized dogs with an enlarged, fatty liver and diabetic children with the same complication. In the first place, in the animals, as Chaikoff and his associates[14] have shown, the lipid content of the blood is low. The blood cholesterol value is low, with almost complete disappearance of the ester fraction. In diabetic patients the blood fat and cholesterol values are usually moderately elevated. In almost every case there is a normal percentage of ester cholesterol, and those few values which are reduced are only slightly so. Furthermore, in animals the giving of raw pancreas, with a reduction in the size of the liver, causes a rise in blood fat and

10. Best, C. H., and Huntsman, M. E.: The Effects of the Components of Lecithin upon Deposition of Fat in the Liver, J. Physiol. **75**:405 (Aug. 10) 1932.

11. Fletcher, J. P.; Best, C. H., and Solandt, O. M.: Distribution of Choline, Biochem. J. **29**:2278 (Oct.) 1935.

12. Best, C. H.; Grant, R., and Ridout, J. H.: The "Lipotropic" Effect of Dietary Protein, J. Physiol. **86**:337 (May 4) 1936.

13. Best, C. H., and Campbell, J.: Anterior Pituitary Extracts and Liver Fat, J. Physiol. **86**:190 (Feb. 8) 1936.

14. Chaikoff, I. L., and Kaplan, A.: The Blood Lipids in Completely Depancreatized Dogs Maintained with Insulin, J. Biol. Chem. **106**:267 (Aug.) 1934.

cholesterol values, together with a rise in the ester cholesterol value.[15] In our diabetic children receiving betaine this did not occur except to a slight extent in 3 cases (cases 7, 30 and 33) and, in general, one finds a decrease rather than an increase in the blood cholesterol value as the diabetes is brought under better control. In the depancreatized dog with enlargement of the liver due to a lack of choline or lecithin, the giving of choline produces along with improvement in the general condition a paradoxic increase in the sugar content of the urine. In the diabetic patient clinical improvement goes hand in hand with reduction of the glycosuria.

It must be remembered that in the diabetic patient the external secretion of the pancreas, although probably impaired in some cases, is by no means entirely lacking, as it is in the depancreatized dog.

4. The possibility exists that to a greater or less extent the hepatomegaly seen in diabetic children may be due to the accumulation of substances other than fat. In the preceding paper we [1] have presented evidence suggesting that glycogen is not primarily responsible and have suggested the possibility that part of the enlargement in some cases may be due to the imbibition of water incident to hydropic degeneration of the hepatic cells.

There has been considerable discussion as to whether or not choline is the constituent of raw pancreas which is responsible for the beneficial effects seen when raw pancreas is fed regularly to the completely depancreatized dog maintained with insulin. Thus, Ralli, Flaum and Banta [16] reported that lecithin was not as effective as raw pancreas in preventing the deposition of fat in the liver of depancreatized dogs. Then Chaikoff and Kaplan [17] found that choline fed to depancreatized dogs was relatively ineffective in influencing the blood cholesterol value as compared with raw pancreas given in amounts containing far less choline (as calculated from the lecithin content). They concluded that the blood lipid factor is not choline. In studies subsequently reported, these workers [18] stated that whereas choline fed to completely depan-

15. Chaikoff, I. L., and Kaplan, A.: The Influence of the Ingestion of Raw Pancreas upon the Blood Lipids of Completely Depancreatized Dogs Maintained with Insulin, J. Biol. Chem. **112**:155 (Dec.) 1935.

16. Ralli, E. P.; Flaum, G., and Banta, R.: The Results of Feeding Lecithin and Pancreas in Depancreatized Dogs on the Liver Fat and Its Saponifiable and Unsaponifiable Fractions, Am. J. Physiol. **110**:545 (Jan.) 1935.

17. Chaikoff, I. L., and Kaplan, A.: Comparative Effects of Pancreas and Choline on Blood Cholesterol of Depancreatized Dog Maintained with Insulin, Proc. Soc. Exper. Biol. & Med. **34**:413 (May) 1936.

18. Kaplan, A., and Chaikoff, I. L.: The Effect of Choline on the Lipid Metabolism of Blood and Liver in the Completely Depancreatized Dog Maintained with Insulin, J. Biol. Chem. **120**:647 (Sept.) 1937.

creatized dogs in large amounts influences the deposition of fat in the liver, its curative action is slow and daily feeding for a long time is required to produce measurable effects on the liver in which a large amount of fat has accumulated. Furthermore, Prohaska, Dragstedt and Harms [19] have stated that the beneficial effect of raw pancreas in preventing or relieving the fatty changes in the liver cannot be accounted for on the basis of its lecithin or choline content, since the amount of these substances required is relatively great. While agreeing with the conclusion just cited, Kaplan and Chaikoff,[18] criticized the methods used by Dragstedt, Prohaska and Harms. The last named workers [20] reported that they had obtained in alcoholic extracts of beef pancreas a substance which they had named lipocaic, which when fed to pancreatectomized dogs maintained with insulin acted in a specific manner to allow survival and to prevent and relieve the deposition of fat in the liver. Results obtained with lipocaic in human beings will be of interest; so far only one report has come to our attention, that of Grayzel and Radwin,[21] who stated that they obtained a decrease in the size of the liver in 3 diabetic children with the giving of lipocaic, whereas careful control of the diet and adequate insulin treatment had previously been unsuccessful. In their preliminary communication no specific values for the size of the liver before or after treatment were given.

Best [22] said he considered that the lipotropic action of raw pancreas may be due to any or all of the following factors: (1) its choline content; (2) its protein content;[12] (3) its enzyme content, allowing for digestion of dietary protein and incidentally for the release of choline from such, and (4) possibly the presence in it of betaine and other substances closely related to choline.[9b] An influence due to pancreatic juice has been denied by Prohaska, Dragstedt and Harms.[19]

Relevant to this discussion is the recent paper of Aylward and Holt.[23] These investigators found no evidence of the presence of a lipotropic factor in pancreas other than choline. Their work was with normal rats rather than depancreatized dogs, however.

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19. Prohaska, J. V.; Dragstedt, L. R., and Harms, H. P.: The Relation of Pancreatic Juice to the Fatty Infiltration and Degeneration of the Liver in the Depancreatized Dog, Am. J. Physiol. **117**:166 (Sept.) 1936.

20. Dragstedt, L. R.; Prohaska, J. V., and Harms, H. P.: Observations on a Substance (a Fat Metabolizing Hormone) Which Permits Survival and Prevents Liver Changes in Depancreatized Dogs, Am. J. Physiol. **117**:175 (Sept.) 1936.

21. Grayzel, H. G., and Radwin, L. S.: Treatment of Hepatomegaly in Juvenile Diabetes Mellitus with a Pancreatic Extract, Proc. Soc. Exper. Biol. & Med. **37**:724 (Jan.) 1938.

22. Best, C. H.: Personal communication to the author; footnotes 9 to 13.

23. Aylward, F. X., and Holt, L. E., Jr.: The Nature of the Lipotropic Agent in Pancreas, J. Biol. Chem. **121**:61 (Oct.) 1937.

SUMMARY

The effect of raw pancreas on hepatomegaly was observed in 2 diabetic children, that of betaine hydrochloride in 12 and that of protamine insulin in 19.

No significant change in the size of the liver was observed concomitant with the use of raw pancreas. With the use of betaine a greater or less diminution was seen in 50 per cent of the 12 patients, and with the use of protamine insulin it was seen in 15, or 78.9 per cent, of the 19 patients. Some diminution in size was observed in 1 of 6 patients in a control series.

The beneficial effect seen with the use of protamine insulin is ascribed to the better control of the diabetic condition.

It is concluded that enlargement of the liver in diabetic children is due in the average case chiefly to poor control of the diabetes and not to a lack of choline or of some other agent derived from raw pancreas.

STUDY OF THE DERANGED CARBOHYDRATE METABOLISM IN CHRONIC INFECTIOUS HEPATITIS

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Hypoglycemia has been the outstanding and most constant result of the disturbed carbohydrate metabolism observed when severe injury of the liver has been found clinically or produced experimentally. It appears to have been established that in the normal organism the presence of the liver is necessary for the maintenance of a normal glycemic level.[1] It has been shown that the liver has at least three separate functions directly concerned with the metabolism of dextrose. These functions are (1) glycogenesis, (2) glycogenolysis and (3) the production of dextrose and the deposition of glycogen from noncarbohydrate precursors (glycogenic amino acids and glycerol fraction of fats). The balance between glycogenesis and glycogenolysis allows the liver to function as a storehouse of readily available dextrose to be delivered into the blood stream in times of need.

From these facts it is apparent that there are several possible explanations for the hypoglycemia observed in cases of severe hepatic injury. That the mechanism is not necessarily analogous to partial or complete removal of the liver is obvious. If glycogenesis alone were impaired, the hypoglycemia noted during fasting could be due to insufficient storage of glycogen in the liver, even though the glycogenolytic function was normal. On the other hand, impaired conversion of glycogen to dextrose (glycogenolysis) could account for hypoglycemia without involving the glycogenic mechanism. This would result in the retention of an abnormally large amount of glycogen in the liver. In the well fed organism it seems unlikely that the hypo-

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1. Mann, F. C., and McGath, T. B.: The Effect of Removal of the Liver on the Blood Sugar Level, Arch. Int. Med. **30**:73 (July) 1922.

glycemia could be explained wholly on the basis of an inability to produce dextrose from noncarbohydrate precursors, since this source yields only a small fraction of the total dextrose of the metabolic mixture. That the simultaneous impairment of two or all of these functions could result in hypoglycemia can be conceded.

Another line of reasoning must not be ignored. It might be argued, purely hypothetically, that the hypoglycemia is the result of increased oxidation of dextrose attending severe hepatic lesions. In support of this conception could be presented those cases of diabetes mellitus reported in the literature [2] in which remarkable improvement or even "cure" has been shown with the development and progression of cirrhosis of the liver. But the literature is devoid of respiratory data to support or refute such a hypothesis. The conclusions have been drawn on the basis of blood sugar levels and glycosuria. Respiratory data, among other factors which preclude such a hypothesis, will be given presently.

It has been demonstrated by Underhill,[3] Bodansky,[4] Izume and Lewis,[5] McIntosh,[6] Cross and Blackford [7] and others that hepatotoxic chemicals such as hydrazine, phosphorus, chloroform, neoarsphenamine and carbon tetrachloride may produce hypoglycemia. Izume and Lewis,[5] using rabbits, showed that in hydrazine poisoning the function of hepatic glycogenesis was impaired. These animals exhibited low blood sugar levels during fasting. After the administration of dextrose the glycogen content of the liver was lower than that of the control animals, and the blood sugar level was higher, indicating an inability of the liver to remove dextrose from the blood stream and to deposit it as glycogen. It was found that the ability of the liver to deposit glycogen after the administration of glycogenic amino acids was also impaired.

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2. Bordley, J., III: Disappearance of Diabetes Mellitus During Development of Cirrhosis of the Liver, Bull. Johns Hopkins Hosp. **47**:113, 1930. Cirrhosis of the Liver, Cabot Case 22261, New England J. Med. **214**:1314, 1936. Strieck, F.: Diabetes und Lebercirrhose, Deutsches Arch. f. klin. Med. **178**:167, 1936.

3. Underhill, F. P.: Influence of Hydrazine upon the Organism, with Special Reference to the Blood Sugar Level, J. Biol. Chem. **10**:159, 1911.

4. Bodansky, M.: Production of Hypoglycemia in Experimental Derangement of the Liver, Am. J. Physiol. **66**:375, 1923; Effect of Chloroform and Phosphorus Poisoning on Carbohydrate Tolerance, J. Biol. Chem. **58**:515, 1923.

5. Izume, S., and Lewis, H. B.: The Influence of Hydrazine and Its Derivatives on Metabolism: II. Changes in the Non-Protein Nitrogenous Constituents of the Blood and in the Metabolism of Injected Glycine in Hydrazine Intoxication, J. Biol. Chem. **71**:33, 1926. Lewis, H. B., and Izume, S.: The Influence of Hydrazine and Its Derivatives on Metabolism: III. The Mechanism of Hydrazine Hypoglycemia, ibid. **71**:51, 1926.

6. McIntosh, R.: Acute Phosphorus Poisoning, Am. J. Dis. Child. **34**:595 (Oct.) 1927.

7. Cross, J. B., and Blackford, L. M.: Fatal Hepatogenic Hypoglycemia Following Neoarsphenamine, J. A. M. A. **94**:1739 (May 31) 1930.

Von Gierke's disease illustrates a type of hepatogenic hypoglycemia the mechanism of which appears to be wholly on the basis of disturbed glycogenolysis. In this disease of childhood, evidenced by hypoglycemia and hepatic enlargement, the liver is found to contain a great excess of glycogen, indicating no disability in its deposition. Thus, an abnormally high glycogen content of the liver associated with chronic hypoglycemia has been interpreted as being due to a deficient glycogenolytic mechanism. Some have attributed this disturbance to a lack or deficiency of an enzyme necessary for the conversion of glycogen to dextrose.

All the clinical cases of chronic hepatogenic hypoglycemia reported have been associated with marked diffuse destructive or degenerative lesions of the liver. In the cases reported by Nadler and Wolfer [8] and by Crawford [9] a primary neoplasm involved most of the hepatic tissue. In those of Josephs [10] and of Judd, Kepler and Rynearson [11] there was severe fatty degeneration of the liver. The case reported by Blackford [7] was due to marked toxic hepatitis following neoarsphenamine therapy. In the case reported by Moore, O'Farrell and Headon [12] there was subacute degenerative hepatitis of unknown etiology. Metabolic studies in clinical cases of this disturbance are few.

The present report consists of detailed studies of 6 patients with chronic hypoglycemia of hepatic origin. Case 1, the metabolic studies of which were continued for over a year, is unique in several ways. The hypoglycemia had been of three years' duration at least. It was shown to be due to ascending infectious hepatitis, the result of chronic purulent cholecystitis. In this case there was remarkable recovery of the disturbed carbohydrate metabolism after removal of the source of the hepatitis.

Case 1.—W. F., a 47 year old laborer, was first admitted to the University Hospital on May 2, 1935, complaining of attacks of unconsciousness. Since March 1934 he had been having periodic attacks of unconsciousness, which always occurred nine to twelve hours after the evening meal and lasted as long as thirty-six hours. The number of attacks averaged two or three each month, although there had been one period of four months without an attack. The attack was characterized by excessive sweating, vomiting and incontinence of

8. Nadler, W. H., and Wolfer, J. A.: Hepatogenic Hypoglycemia Associated with Primary Liver Cell Carcinoma, Arch. Int. Med. **44**:700 (Nov.) 1929.

9. Crawford, W. H.: Hypoglycemia with Coma in a Case of Primary Carcinoma of the Liver, Am. J. M. Sc. **181**:496, 1931.

10. Josephs, H.: Spontaneous Hypoglycemia in Childhood, Am. J. Dis. Child. **38**:746 (Oct.) 1929.

11. Judd, E. S.; Kepler, E. J., and Rynearson, E. H.: Spontaneous Hypoglycemia: Two Cases with Fatty Metamorphosis of the Liver, Am. J. Surg. **24**:345, 1934.

12. Moore, H.; O'Farrell, W. R., and Headon, M. F.: Spontaneous Hypoglycemia Associated with Hepatitis, Brit. M. J. **1**:225, 1934.

urine and feces. There were no convulsions. The attack would end gradually, but the patient would remain disoriented for many hours. He would have no memory of the entire incident. There had been a gradual reduction in weight, from 154 to 130 pounds (from 70 to 59 Kg.), in three years. There were no other complaints.

In 1924 a ruptured colonic diverticulum was repaired; in 1932 subtotal thyroidectomy was performed for nontoxic goiter. There had never been symptoms referable to either the gallbladder or the liver.

Physical, neurologic and laboratory examinations revealed no abnormalities except mild secondary anemia. On discharge no etiologic diagnosis was made.

He returned on Jan. 6, 1936, stating that his attacks had continued at about the same rate. The local physician suggested the presence of an intracranial lesion, since on one occasion an attack had been quickly terminated by the use of 50 per cent solution of dextrose intravenously.

The physical examination again showed no significant abnormality. The urine was normal. The Kahn test gave a negative reaction. Examination of the blood showed macrocytosis of the red blood cells, a color index of more than 1 and a normal amount of hemoglobin. Roentgenograms of the skull showed no abnormality. Several spinal punctures showed normal spinal fluid under normal pressure. The basal metabolic rates were found to be —13 per cent and —3 per cent, respectively, on two occasions. A cholecystogram showed slight visualization of the gallbladder, with possible stone. The bilirubin value was 2.5 mg. per thousand cubic centimeters of blood.

At this point our metabolic studies were begun. A respiration chamber[13] employing the principle of continuous indirect calorimetry by the open circuit method was used to obtain respiratory data. Frequent checks with alcohol demonstrated that the method was capable of determining over 99 per cent of the gaseous exchange. Blood sugar values were determined by the Benedict[14] method and urinary nitrogen values by the Kjeldahl method. Serum protein values were determined by the micro-Kjeldahl method, direct nesslerization being employed and appropriate correction being made for nonprotein nitrogen.[15]

The patient was kept in bed and given a diet extremely low in carbohydrate (1,600 calories; 17 Gm. of carbohydrate and 50 Gm. of available dextrose). The following morning and for five successive mornings he was found to be disoriented and semicomatose or totally unconscious. The blood sugar values during fasting ranged from 14 to 18 mg. per hundred cubic centimeters. Rapid relief was obtained by the administration of dextrose intravenously.

The following groups of laboratory studies, the numerical data of which will be seen in the accompanying charts, seemed to indicate that the hypoglycemia was on the basis of impaired hepatic function:

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13. Newburgh, L. H.; Johnston, M. W.; Wiley, F. H.; Sheldon, J. M., and Murrill, W. A.: A Respiration Chamber for Use with Human Subjects, J. Nutrition **13**:193, 1937.

14. Benedict, S. R.: The Analysis of Whole Blood: II. The Determination of Sugar and of Saccharoids (Non-Fermentable, Copper-Reducing Substances), J. Biol. Chem. **92**:141, 1931.

15. Campbell, W. R., and Hanna, M. I.: Short Method for Determining Albumin-Globulin Ratios in Human Serum, Tr. Roy. Soc. Canada (Sect. V., Biol. sc.) **25**:29, 1931. Wu, H.: New Colorimetric Method for Determination of Plasma Proteins, J. Biol. Chem. **51**:33, 1922. Koch, F. C., and McMeekin, T. L.: A New Direct Nesslerization Micro-Kjeldahl Method and a Modification of the Nessler-Folin Reagent for Ammonia, J. Am. Chem. Soc. **46**:2066, 1924.

1. Dextrose tolerance tests showed an impaired ability to remove absorbed dextrose from the blood stream in the normal length of time. This led to a high delayed plateau curve similar to that seen in the diabetic state. The blood sugar levels during fasting, however, at the beginning of the tests were abnormally low. Such curves can be produced experimentally by hepatic injury.[16]

2. Respiratory data indicated that the oxidation of dextrose was normal both in the fasting state and after the ingestion of dextrose. This demonstrated that the delay in removing absorbed dextrose from the blood stream was due not to decreased oxidation of dextrose but to impaired glycogenesis. Further, these data indicated that the low blood sugar levels of the fasting state were not accompanied by increased oxidation of dextrose, as would be expected in hyperinsulinism.[17] Together these observations suggested that the low blood sugar levels of the fasting state were brought about by impaired glycogenesis and perhaps impaired glycogenolysis.

3. Bromsulphalein excretion tests showed retention of 90 and 70 per cent of the dye (bilirubin, 2.5 mg. per thousand cubic centimeters of blood).

4. Total serum protein values were abnormally low, with inversion of the albumin-globulin ratio.

5. Macrocytosis of the red blood cells was marked.

6. Galactose tolerance was impaired.

Before comparing the preoperative and the postoperative data we shall describe the data relative to the operative treatment. Exploratory laparotomy was done on March 9 by Dr. F. A. Coller. The pancreas was carefully examined and was found to be grossly normal. The liver was of normal size but abnormally pale. Its entire surface was granular, with nodules about 2 mm. in diameter. The gallbladder was distended and contained several large stones and 2 or 3 ounces (60 to 90 cc.) of thick yellow pus. The gallbladder was removed, and a specimen of the liver was taken for biopsy. The pathologist reported evidence of cholelithiasis. A large, soft, pigmented calculus appeared to be made up almost entirely of inspissated bile pigment. There was active purulent cholecystitis with areas of ulceration. Granulation tissue was present in the wall of the gallbladder. The pigment masses in the lumen were of the same nature as those seen in the calculus. Biopsy of the liver showed active chronic cholangiolitis, biliary cirrhosis, cloudy swelling and fatty infiltration but no neoplasm. Figure 1 shows a section of the specimen of the liver.

The accompanying charts, comparing the preoperative data with those obtained during a nine month postoperative period, indicate remarkable improvement in the capacity of the liver to deal with dextrose. Simultaneously, the other indications of abnormal hepatic function disappeared.

The accompanying table shows the respiratory metabolism of the patient and that of the control subjects under a variety of conditions. The patient's ability to oxidize dextrose was neither decreased nor increased over the normal either before or after operation. The disturbance, then, could not be said to be one of overoxidation of dextrose.

Figure 2 demonstrates the gradual return of the glycogenic function of the liver in the postoperative period. The absorbed dextrose was then being removed

16. Coller, F. A., and Troost, F. L.: Glucose Tolerance and Hepatic Damage, Ann. Surg. **90**:781, 1929. Cross and Blackford.[7]

17. Liu, S. H.; Loucks, H. H.; Chou, S. K., and Chen, K. C.: Adenoma of Islet Cells with Hypoglycemia and Hyperinsulinism: Report of Case with Studies on Blood Sugar and Metabolism Before and After Operative Removal of the Tumor, J. Clin. Investigation **15**:249, 1936.

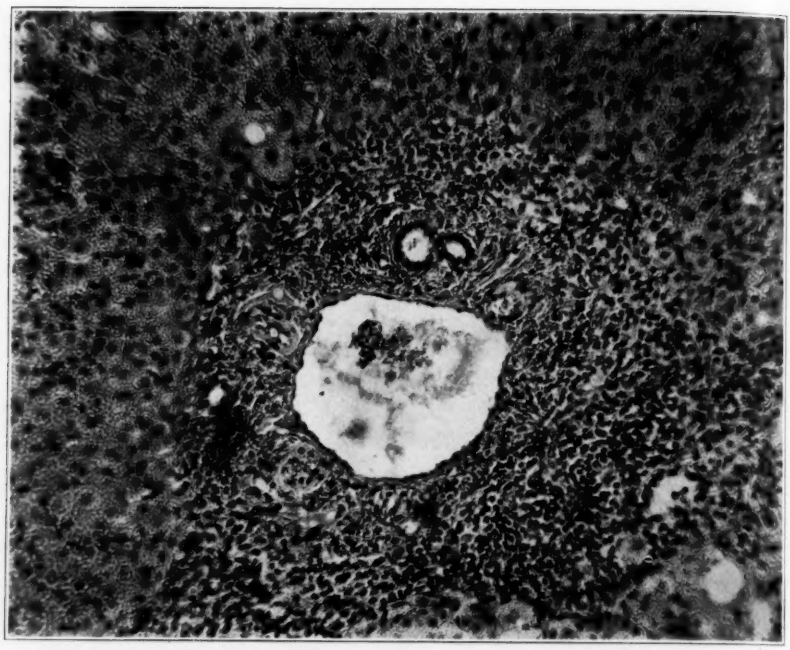

Fig. 1 (case 1).—Section of the specimen from the liver removed for biopsy.

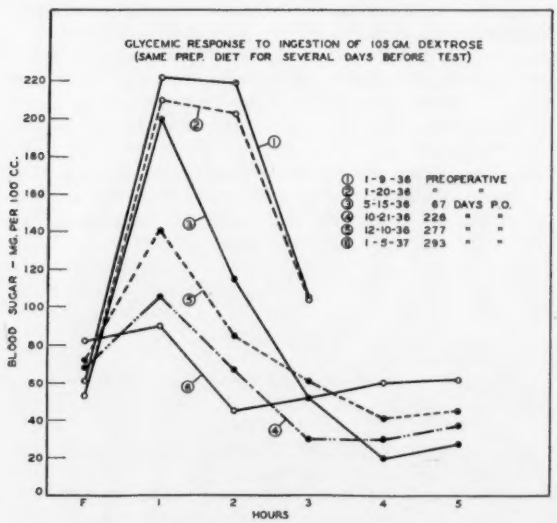

Fig. 2 (case 1).—Chart showing the blood sugar values.

from the blood stream rapidly. Note that as time went on the level of the blood sugar during fasting rose from 51 to 81 mg. per hundred cubic centimeters, the patient having been taking the same diet for several days before each test. Note also that the blood sugar level at the end of the fifth hour showed a progressive rise. These observations indicated gradual improvement in the patient's ability to maintain a blood sugar level closer to the normal. It is apparent, however, that there was still some active disturbance in the function of glycogenolysis. For curve 4, for example, showing rapid removal of dextrose from the blood stream, there must have been an impaired glycogenolytic mechanism which blocked the release of dextrose from the liver even in time of need. The

Carbohydrate Oxidized in Four Hours

		Dietary Preparation (3 Days Before Test)						
Date	Subject	Calories	Carbohydrate, Gm.	Dextrose Ingested in Chamber, Gm.	Carbon Dioxide Produced, Liters	Oxygen Absorbed, Liters	Urinary Nitrogen, Gm.	Dextrose Oxidized in Chamber, Gm.
2/28/36	Case 1	2,800	150	50	52	61	1.5	36
	Control	2,750	100	50	56	68	2.3	31
	Control	2,750	100	50	51	57	2.4	42
	Control	2,750	200	50	56	63	2.5	44
	Control	2,750	200	50	51	58	1.9	37
4/13/37	Case 2	2,400	200	50	67	79	3.6	39
5/28/36	Case 1	3,000	500	0	61	76	2.0	29
	Control	4,200	500	0	62	75	2.1	33
6/29/36	Case 1	2,600	200	0	59	76	1.9	19
	Control	2,750	200	0	47	59	2.2	16
	Control	2,750	200	0	48	61	2.0	18
7/ 1/36	Case 1	2,600	200	200	67	70	1.9	68
	Control	2,750	200	200	66	68	2.8	65
	Control	2,750	200	200	68	75	1.6	63
7/24/36	Case 3	2,600	100	100	54	61	1.9	45
	Control	2,600	100	100	55	61	2.0	49
1/26/37	Case 6	2,400	200	100	55	58	1.6	54
	Control	2,750	200	100	56	60	2.3	54
	Control	3,000	200	100	59	69	1.7	49
	Control	3,000	200	100	60	67	2.1	52

improvement in glycogenolysis appeared to lag considerably behind that of glycogenesis.

Figure 3 again demonstrates the disturbed glycogenolytic mechanism. Although the ability to maintain a normal blood sugar level during fasting had returned, there was little change in the glycemic response to the injection of epinephrine.

Figure 4 shows the average blood sugar levels during fasting maintained by the patient for progressive periods over the year of study. For each period the daily blood sugar value during fasting was determined to obtain the average for the period. Periods VIII, IX, XI, XII and XIV, all falling in the postoperative period, while the patient was eating a general diet (about 300 Gm. of carbohydrate daily), showed a return of the ability to maintain a normal blood sugar level during fasting. Period I, the preoperative period, with a general diet, showed an average fasting level of 58 mg. In periods VI and VII improvement continued, in spite of the fact that the carbohydrate of the daily diet was reduced from

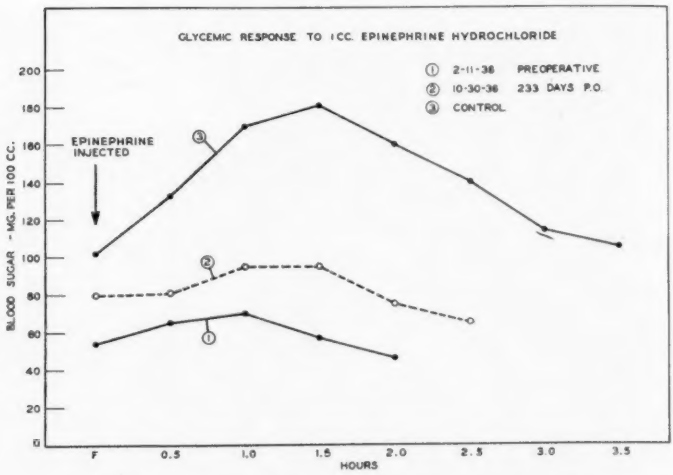

Fig. 3 (case 1).—Chart showing the blood sugar values.

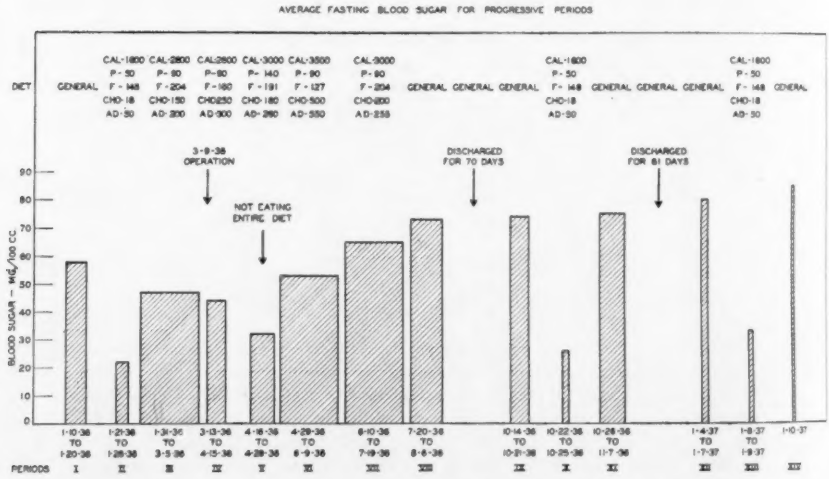

Fig. 4 (case 1).—Chart showing the average levels of the blood sugar during fasting for progressive periods.

500 to 200 Gm. Periods II, X and XIII represented the response to a sharply restricted intake of carbohydrate. Although unquestioned improvement had taken place in the postoperative period, this appeared to be the most sensitive test of complete recovery. Without this observation there was little to indicate any abnormality in the metabolism of carbohydrate at this stage of recovery. In fact, by this time all the other evidence suggesting abnormal function of the liver had disappeared.

The progressive improvement in the protein level of the blood serum is seen in figure 5. The values for total serum protein returned to their normal level, and the albumin-globulin ratio, which had been inverted, became normal. It should be noted here that the bromsulphalein excretion was normal in the last three determinations: August 7, 15 per cent; October 14, 20 per cent, and December 10, 18 per cent retention of the dye. The last galactose tolerance test,

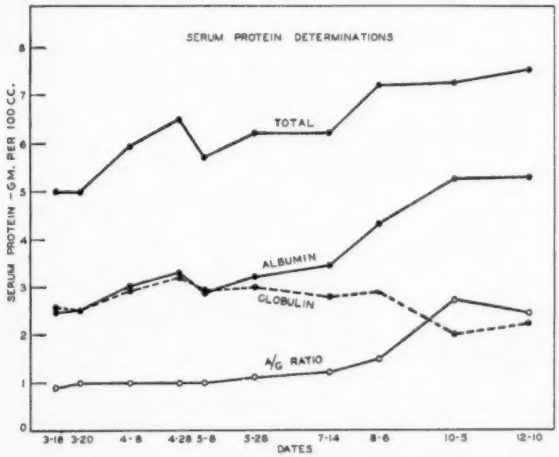

Fig. 5 (case 1).—Chart showing the values for blood protein.

on October 14, gave a normal result. Macrocytosis of the red blood cells disappeared gradually, and on October 14 the blood was considered normal.

There have been no spontaneous hypoglycemic attacks since operation. Since the completion of these studies the patient has been carrying on his normal activities in apparent good health.

CASE 2.—F. D., a 55 year old farmer, was admitted to the University Hospital on March 31, 1936. His chief complaints were of swelling of the neck and attacks of unconsciousness. He had been a resident of Michigan all his life and had noted gradual enlargement of the thyroid gland for thirty years. There was nothing to suggest thyrotoxicosis.

For three years there had been attacks of unconsciousness, eight in all, each occurring in the early morning. Each was characterized by premonitory weakness and instability. This was immediately followed by a period of unconsciousness, lasting from a few minutes to several hours. There were no convulsions. Profuse

sweating was associated with the attack. He had found that eating candy would ameliorate or prevent an attack. There had been two such episodes in the past year.

The past history contributed nothing of significance. There had never been symptoms referable to either the liver or the gallbladder.

Physical examination showed a well developed, well nourished middle-aged man who did not appear ill. There was a medium-sized adenomatous goiter. The heart was of borderline size. The chest was otherwise normal. The blood pressure was 170 systolic and 115 diastolic. The liver and spleen were not palpable. There were no other abnormal physical findings.

The urine was normal, and the Kahn test gave a negative reaction. On repeated examinations the red blood cells showed definite macrocytosis, there was a color index above 1 and the hemoglobin content was normal. This suggested hepatic disease to the hematologist. The blood was otherwise normal. A cholecystogram demonstrated complete nonvisualization of the gallbladder. Roentgenograms of the skull showed no evidence of intracranial disease. The basal metabolic rates were +15 per cent and +13 per cent, respectively, on two occasions. The bilirubin content of the blood was 1 mg. per thousand cubic centimeters. The bromsulphalein test gave a normal result. The serum protein values were: 6.9 per cent, total protein; 3.8 per cent, albumin, and 3.1 per cent, globulin; and the albumin-globulin ratio was 1.2. The results of the dextrose tolerance tests, in milligrams per hundred cubic centimeters, were as follows:

		Hours			
Date	Fasting	1	2	3	4
4/1/36	50	135	202	142	...
4/6/36	65	200	242	184	148

The patient was kept in bed and fed a low carbohydrate diet (1,600 calories; 17 Gm. of carbohydrate). For the next three successive days the blood sugar values during fasting were 26, 28 and 26 mg. per hundred cubic centimeters, respectively. The patient was semicomatose when the blood sugar was at these levels and quickly recovered with the administration of dextrose intravenously.

The respiratory data for this patient are given in the accompanying table. When these data are compared with those for the controls, it is found that the oxidation of dextrose by the patient was normal under the conditions studied.

The patient refused operation and has not been heard from since discharge from the hospital.

Comment.—The evidence presented seems to justify the inclusion of this case in the group of cases of hepatogenic hypoglycemia. It appears that the disturbance in carbohydrate metabolism was similar to that described in case 1 and that the hypoglycemia could not be explained on the basis of increased oxidation of dextrose.

CASE 3.—W. S., a 50 year old laborer, came to the University Hospital on July 8, 1936, complaining of peculiar attacks of disorientation of one year's duration. The attacks would come on at any time of the day or night and recently had been occurring two or three times a week. Consciousness was not completely lost in any of the attacks. There was premonitory blurring of vision, followed by tinnitus, marked apprehension, bobbing of the head from side to side and occasionally involuntary muscular twitching. There were no other complaints.

Since late childhood there had been periodic attacks of jaundice lasting several weeks to two months. This situation occurred about once a year, the longest period of freedom having been four years. During these periods the stools were clay colored, and the urine was dark. There was no associated dyspepsia or abdominal pain.

Twelve years previously he had a primary penile sore, and weekly antisyphilitic treatments were given for one year.

Physical examination showed a well nourished middle-aged man who did not appear ill. There was faint icterus of the scleras and skin. The pupils reacted sluggishly to light. There was a generalized shotty lymphadenopathy. The chest was normal. The blood pressure was 115 systolic and 80 diastolic. A firm margin of the liver could be felt 3 cm. below the right costal margin. The spleen was not palpable. The reflexes were normal.

Laboratory examination showed that the urine was normal. The blood showed marked macrocytosis, a color index above 1 and a normal amount of hemoglobin. The Kahn test of the blood showed a 1 plus reaction. The spinal fluid was normal in all respects. The bilirubin content of the blood was 17 mg. per thousand cubic centimeters. The bromsulphalein test showed 80 per cent retention of the dye. The serum protein values were: 7.4 per cent, total protein; 3.4 per cent, albumin, and 4 per cent, globulin; and the albumin-globulin ratio was 0.8. A cholecystogram demonstrated complete nonvisualization of the gallbladder. The results of the dextrose tolerance tests, in milligrams per hundred cubic centimeters, were as follows:

		Hours				
Date	Fasting	1	2	3	4	4½
7/ 7/36	78	148	88	32	45	..
7/14/36	91	230	184	88	28	32

For three days after the giving of a restricted carbohydrate diet the blood sugar value during fasting was 78, 80 and 53 mg. per hundred cubic centimeters, respectively.

The respiratory data for this case are given in the accompanying table.

On August 1 exploratory laparotomy was done. A considerable amount of clear free fluid was present in the abdominal cavity. The liver was considerably enlarged and firm. The surface was diffusely nodular, suggesting cirrhosis. The spleen was not enlarged. The pancreas was firm and indurated. The gallbladder was distended and tense. No stones were felt. The common duct appeared normal. Specimens of the liver and pancreas were taken for biopsy. Cholecystogastrostomy was done with the hope that internal drainage of the biliary sac might be accomplished. Postoperatively the patient went into shock and died, in spite of all supportive measures.

The pathologist gave the following report: The specimen from the liver showed active chronic hepatitis, with active regeneration of the hepatic cells, leading to an early stage of nodular cirrhosis. The hepatic cells were swollen, with marked vacuolation of small groups of cells. The hepatic cells showed a rich but highly variable content of glycogen. Many cells contained sufficient glycogen to result in a deep red staining reaction, while other cells were devoid of stainable carbohydrate. The gallbladder showed chronic cholecystitis with fibrosis of the wall. The specimen from the pancreas contained small but numerous islands. The external secretory portion of the pancreas showed slight

fatty atrophy. Examination of the whole organs showed essentially the same picture. Careful sectioning revealed no evidence of pancreatic neoplasm.

Comment.—In this case the pathologic changes were similar to those described in case 1. Both the pathologic changes and the disturbance in carbohydrate metabolism were less severe. The patient's ability to store dextrose as glycogen in the liver, although somewhat impaired, appeared to be much less affected than in the 2 preceding cases. This was demonstrated by the dextrose tolerance curves and by the presence of a considerable store of glycogen in the liver. The function of rapid glycogenolysis seemed to have been impaired and could account for the periodic hypoglycemic episodes. It appears evident that the hypoglycemia, which was well established by the fourth hour in both dextrose tolerance curves, could not be explained on the basis of increased oxidation of dextrose in the four hour period (table).

CASE 4.—F. P., a 66 year old farmer, was admitted to the University Hospital on Sept. 9, 1936, in deep coma. The history was meager and unreliable, being obtained from relatives. About six months before entry he had begun to complain of intermittent pain in the right upper quadrant of the abdomen. There had been no obvious jaundice. His appetite had been decreasing, and there had been gradual loss of weight for three months. Edema of the lower extremities had begun about two months before entry and persisted. Extreme weakness had been of two weeks' duration. The night before entry he had gradually lapsed into coma. There had been no previous periods of unconsciousness. The past history was not obtainable.

Examination showed a malnourished man of late middle age who was in deep coma. There was moderate pallor but no icterus. The temperature was 94 F., the pulse rate 68 and the respiratory rate 16. The blood pressure was 100 systolic by palpation. The extremities were cold, and the patient was perspiring profusely. The pupils reacted normally to light. All the tendon reflexes were absent, and no abnormal reflexes were obtained. The heart was moderately enlarged. The lungs were clear. A mass the size of an orange, hard and freely movable, was felt deep in the right upper quadrant of the abdomen. The liver and spleen could not be felt. There was edema of the lower extremities, extending to the groin and including the genitalia.

The urine was normal. The blood showed marked secondary anemia, with a hemoglobin value of 38 per cent (Sahli). The Kahn test gave a negative reaction. The nonprotein nitrogen content was 29.6 mg. per hundred cubic centimeters. The carbon dioxide–combining power was 66 volumes per cent. The blood sugar value was 14 mg. per hundred cubic centimeters.

After 100 cc. of 50 per cent solution of dextrose was given intravenously the patient became conscious and rational on questioning. The temperature, pulse rate and respiratory rate became normal, but the blood pressure remained low. A continuous intravenous infusion of 5 per cent solution of dextrose was given until 3 p. m. the following day. The patient remained alert and cooperative. At 10 a. m. the next day profuse sweating occurred, with a rectal temperature of 95 F., and he lapsed into coma. The blood sugar value at this time was 20 mg. per hundred cubic centimeters. Again, a continuous intravenous injection of dextrose was given for the next fifteen hours, with the same dramatic result.

Eight hours later the patient was again in coma, with a blood sugar reading of 12 mg. per hundred cubic centimeters. Dextrose again helped, but generalized anasarca progressed rapidly, and on September 14 respirations ceased.

Postmortem examination showed marked anasarca and polyserositis. There were terminal hypostatic pneumonia and cardiac dilatation. A large, friable, fungating, mucoid mass, found to be arising from the duodenal mucosa, completely encircled the duodenum. It had grown into the head of the pancreas. The remainder of the pancreas appeared normal. The ampulla of Vater was patent, and bile was present in the duodenum. The common bile duct was greatly dilated, however. The liver was of normal size, and the gallbladder was grossly normal.

Microscopically, the mass was found to be adenocarcinoma mucosum, primary in the region of the ampulla of Vater. The pancreas showed direct extension of the neoplasm into its own substance. The islands of Langerhans were small. There was no evidence of neoplastic pancreatic tissue. The liver showed chronic passive congestion and mild biliary obstruction. There was increased stroma in the islands of Glisson, with lymphocytic proliferation and infiltration in the bile ducts. Staining for fat showed no lipoidosis. The gallbladder revealed thickening and inflammatory infiltrations in its wall, fragments of biliary calculi and chronic cholecystitis.

Comment.—Although no respiratory data were obtainable in this case, the pathologic changes indicated that the hypoglycemia was on the basis of hepatic dysfunction. The changes in the gallbladder and liver were similar to those observed in the previous cases.

We believe that the hypoglycemic status was brought to light in this case by the sharply restricted intake of food, which, in turn, was the result of an intestinal neoplasm. The hypoglycemic response was similar to that which we have produced with a restricted diet. It seems probable that the functional hepatic damage was the result of the involvement of the biliary tract. It is noteworthy in this case, as in the previous ones, that the degree of hepatic damage histologically was not extremely marked. The functional capacity, however, as regards carbohydrate metabolism, was greatly affected.

Case 5.—T. F., a 52 year old housewife, was admitted to the University Hospital on Nov. 10, 1937, complaining of jaundice. For about six years she had had symptoms typical of dyspepsia due to disorder of the gallbladder. Three years previously there began to occur true biliary colic associated with transient jaundice. On Oct. 5, 1936, cholecystectomy was done at the Foote Memorial Hospital, in Jackson, Mich. Purulent cholecystitis and cholelithiasis were present at that time. A drainage tube was inserted, and pus and bile continued to drain for seven weeks postoperatively. The wound closed, and the patient felt well again until April 1937, when she noticed the onset of progressive painless jaundice. Nausea, anorexia and lethargy supervened. Clay-colored stools and dark urine became constant. Profuse sweats occurred frequently in the early hours of the morning for a month before entry. There had been no significant loss of weight.

The past history contributed little.

Physical examination revealed a poorly nourished middle-aged woman who appeared chronically ill. There was moderate generalized icterus. The tem-

perature was 102 F., the pulse rate 96 and the respiratory rate 20. The heart and lungs were normal. The blood pressure was 120 systolic and 80 diastolic. The abdomen showed a well healed right rectus excision. The liver was extended about 3 cm. below the right costal margin but was not tender. The spleen was not felt. There was no other significant physical finding.

The urine was normal except for the presence of a large amount of bile. The stools were acholic. Except for mild secondary anemia the blood was normal. The Kahn test gave a negative reaction. The bilirubin content of the blood was 27 mg. per hundred cubic centimeters (direct). The serum protein values were: 6.6 per cent total protein, 2.4 per cent albumin and 4.2 per cent globulin; and the albumin-globulin ratio was 0.6. On November 12 the dextrose tolerance test showed the following values: fasting, 60; first hour, 114; second hour, 120; third hour, 75, and fourth hour, 33 mg., per hundred cubic centimeters.

On November 20 laparotomy was done. The pancreas was normal. The liver had an irregular nodular surface suggesting biliary cirrhosis. The common bile duct was involved in a mass of adhesions and was completely constricted. No type of reconstruction was possible; catheter drainage to the outside was instituted. A specimen of the liver was taken for biopsy, and the pathologist reported that it showed ascending cholangitis and beginning biliary cirrhoses.

CASE 6.—T. R., a 51 year old housewife, was first seen at the University Hospital on Oct. 18, 1935, complaining of attacks of weakness, staggering and tinnitus. These attacks had come on periodically for five years at any time of the day. At the onset the local physician found sugar in the urine, and he restricted the intake of carbohydrate somewhat. The glycosuria rapidly disappeared, but the attacks (which were interpreted as hysterical) continued. A severe attack occurred eight months before entry. There had never been loss of consciousness, polyuria, polydipsia, polyphagia or spontaneous loss of weight. In the past year she had lost 35 pounds (16 Kg.) by caloric restriction.

Physical examination revealed a well nourished middle-aged woman who did not appear ill. The only abnormal physical finding was slight enlargement of the liver, the edge being firm and extending 2 cm. below the right costal margin. There was tenderness to pressure in the right upper quadrant of the abdomen.

The urine and blood were normal, and the Kahn test gave a negative reaction. A cholecystogram showed normal visualization of the gallbladder, with a solitary semiopaque stone. There was abnormal rounding of the hepatic margin. A dextrose tolerance test showed the following values: fasting, 72; first hour, 224; second hour, 194, and third hour, 132 mg., per hundred cubic centimeters. All the specimens of urine except the one taken during fasting showed glycosuria.

The patient was discharged on November 14 with a maintenance dietary regimen for diabetes without insulin. She was considered to have extremely mild diabetes, since she tolerated a normal diet without glycosuria.

A year later, on Nov. 5, 1936, she returned, having had no glycosuria for six months with an unrestricted diet. She complained bitterly of attacks similar to those previously described but more severe. She now called these attacks "the jitters." During the attacks, which came on most frequently in the morning, she would experience "inward and outward trembling," profuse sweating and intense hunger. She found that food relieved the attacks quickly. There had been infrequent attacks of pain in the right upper quadrant of the abdomen but no jaundice.

The physical findings were the same as those of the previous year.

A cholecystogram was made and disclosed faint visualization of the gallbladder, in which was seen a solitary semiopaque stone. It was noted that there had been progressive downward enlargement of the liver since the earlier examination. The tabulated results of the dextrose tolerance tests will be given later.

On the third, fourth and fifth days of the restricted carbohydrate diet, the blood sugar readings during fasting were 42, 57 and 47 mg. per hundred cubic centimeters, respectively. The bromsulphalein excretion and the values for blood bilirubin, serum protein and red blood cells were normal. Two months later this same test gave blood sugar levels of 48 and 46 mg. per hundred cubic centimeters.

On March 3, 1937, cholecystectomy was performed. The pancreas was grossly normal. The liver was grossly enlarged and exhibited a finely granular surface. The gallbladder was moderately thickened and contained a large stone. The gallbladder was removed, and a specimen of the liver was taken for biopsy.

The pathologist reported that examination of the gallbladder showed cholelithiasis, a solitary concretion being present. There was slight chronic cholecystitis, with slight cholesterosis of the mucosal folds. The liver showed slight chronic interlobular hepatitis, with lymphocytic infiltration of the islands of Glisson. The inflammatory changes were relatively slight in the specimen studied. Staining showed irregular distribution of visible fat, the most marked storage being in the lobules which also showed the most marked inflammation. Staining for glycogen showed an abundant deposit, which was most marked around the central veins.

The results of the dextrose tolerance tests, in milligrams per hundred cubic centimeters, were as follows:

		Hours				
Date	Fasting	1	2	3	4	5
10/22/36	72	224	194	132	..	..
1/14/37	77	205	130	56	49	..
3/ 3/37	Operation					
9/14/37	96	222	100	55	61	71

On Sept. 15, 1937, she was again given the restricted carbohydrate diet. After three days the blood sugar value during fasting fell to 38 mg. per hundred cubic centimeters. Preoperative respiratory data indicated that the low blood sugar values were not accompanied by increased oxidation of dextrose (table).

Comment.—In this case it appeared that, again, the glycogenolytic mechanism was the most seriously involved and that, although in the later stages the liver appeared to be capable of rapid glycogenosis, glycogenolysis remained impaired. The presence of large amounts of glycogen in the biopsy material from the liver also favored this interpretation. It was evident that glycogenesis was delayed earlier. This gave rise to the high plateau type of dextrose tolerance curve, which led to an erroneous diagnosis of diabetes mellitus. Spontaneous glycosuria had been found on several occasions. Oxidation of dextrose was found to be normal, however.

It is probable that those cases in which a diagnosis of diabetes mellitus has been made and the patient has been said to recover with the development of cirrhosis of the liver [2] were not cases of diabetes

mellitus in the true sense. It is more likely that the original hyperglycemia and glycosuria were early manifestations of hepatic dysfunction and that the hyperglycemia was due not to decreased oxidative ability but to delayed glycogenesis.

COMMENT

An investigation was made to determine the nature of the disturbed carbohydrate metabolism associated with chronic ascending infectious hepatitis. Six patients were studied. All exhibited periods of spontaneous hypoglycemia. The glycemic response to ingested dextrose was grossly abnormal in several ways. A short period of fast or of carbohydrate restriction resulted invariably in severe hypoglycemia. Data obtained by indirect calorimetry indicated normal oxidation of dextrose under all of a variety of conditions. Besides the disturbance in carbohydrate metabolism, there were clinical and laboratory indications that other functions of the liver were also impaired. Microscopic examination of biopsy or autopsy material in these cases showed different stages of the same pathologic picture. Chronic cholecystitis and ascending infectious hepatitis leading to early biliary cirrhosis constituted the common pathologic change. Examination of the pancreas showed no abnormality either at operation or at autopsy.

We believe that this disturbance in carbohydrate metabolism, although common, is frequently unrecognized or wrongly interpreted. In the early stage the glycogenic function of the liver appears to be seriously impaired. This conclusion is reached as follows: In the well nourished normal organism, absorbed dextrose is disposed of by its simultaneous oxidation in the tissues and by the conversion and deposition of dextrose as glycogen in the liver and to a lesser degree in the muscles. Since our patients showed a hyperglycemic response after ingestion of dextrose and since they were shown to oxidize dextrose at the normal rate under the same conditions, the excess dextrose in the blood stream must be explained by impaired glycogenesis. We believe that this impairment in glycogenesis is one of rate rather than one of total disability since the blood sugar returns to the fasting level four to five hours after ingestion of dextrose and since removal of dextrose is not explained by increased oxidation. The slow rate of glycogenesis accounts for the prolonged hyperglycemia.

This delayed removal from the blood stream of absorbed carbohydrate results in postprandial hyperglycemia and glycosuria. Often this phenomenon has led to a diagnosis of diabetes mellitus (see cases 1 and 6). Our demonstration of normal oxidation of dextrose during this hyperglycemic period makes this diagnosis untenable. Recovery of the glycogenic function appears to parallel the disappearance of the active infection.

With the involvement of the glycogenolytic function of the liver, periods of hypoglycemia become manifest. This situation may be easily mistaken for hyperinsulinism. Respiratory data obtained during the hypoglycemic phase of this disturbance indicate that the low blood sugar levels are not the result of overoxidation of dextrose, as is the case in true hyperinsulinism. That in proved hyperinsulinism, overoxidation of dextrose can be demonstrated by respiratory studies has been shown by Liu, Loucks, Chou and Chen.[17]

It seems, then, that hyperglycemia and glycosuria simulating diabetes mellitus may be a manifestation of one phase of hepatic dysfunction and that periodic spontaneous hypoglycemia may be the manifestation of further hepatic injury in the same patient at different times in the course of hepatitis. This suggests that the hypothetic conception of "dysinsulinism," propounded by Harris [18] to explain hyperglycemia in one period and spontaneous hypoglycemia in another in the same patient, is probably not the true underlying physiologic mechanism involved in many cases. Since oxidation of dextrose is normal in both the hyperglycemic and the hypoglycemic phases, it appears that hypoinsulinism alternating with hyperinsulinism is not the explanation.

Harris [19] also stressed the fact that many patients with hyperinsulinism give a previous history of glycosuria. It should be recalled that close to 50 per cent of the patients operated on for hyperinsulinism have failed to disclose pancreatic abnormality.[20] It is conceded that a tiny tumor of the islet tissue may be easily missed at operation. But in those cases in which partial or subtotal pancreatectomy has been done when a pancreatic tumor has not been found, the results have been notoriously unsuccessful in relieving the hypoglycemia. Hepatogenic hypoglycemia seems a more likely explanation. Even though the anatomic changes in the liver may be slight, the presence of chronic biliary infection may lead to marked functional disturbances in the metabolism of carbohydrate.

A short period of fast or sharp restriction of the intake of carbohydrate gave rise in our patients to extremely low blood sugar levels. It appears that this response to carbohydrate restriction is a sensitive

18. Harris, S.: Nomenclature of Disorder of Insulin Secretion: Diabetes Mellitus, Hyperinsulinism and Dysinsulinism; Analytical Review of Data Relevant to Classification and Terminology of Secretory Disorder of the Islets of Langerhans of the Pancreas, Ann. Int. Med. **7**:1084, 1934.

19. Harris, S.: (*a*) Hyperinsulinism, a Definite Disease Entity: Etiology, Pathology, Symptoms, Diagnosis, Prognosis and Treatment of Spontaneous Insulogenic Hypoglycemia (Hyperinsulinism), J. A. M. A. **101**:1958 (Dec. 16) 1933; (*b*) footnote 18.

20. Wilder, R. M., in discussion on Harris,[19a] p. 1964. Conn, J. W.: The Advantage of a High Protein Diet in Spontaneous Hypoglycemia, J. Clin. Investigation **15**:673, 1936.

test of the ability of the liver to deal normally with carbohydrate. When all other indications of impaired hepatic function had returned to normal, this test still demonstrated an inability of the organism to maintain a normal blood sugar level during fasting.

In this type of hepatic dysfunction, all the classic symptoms of disease of the gallbladder or liver may be absent. This is well illustrated in several of our cases. Hence, patients who suffer from periodic spontaneous hypoglycemia or whose dextrose tolerance curves are suggestive of diabetes in association with a low blood sugar level during fasting should be investigated for the presence of infection of the biliary tract.

The cases of chronic hepatogenic hypoglycemia reported in the literature have been associated with incurable destructive or degenerative lesions of the liver. It is evident from our experience that the condition described may be greatly helped or even alleviated to the stage of clinical cure if the diagnosis of infectious hepatitis is made early and if appropriate surgical treatment is instituted.

CONCLUSIONS

A syndrome is described which is characterized by the presence of low blood sugar values during fasting, postprandial hyperglycemia and glycosuria and periodic attacks of spontaneous hypoglycemia.

Various stages of chronic ascending infectious hepatitis constitute the common pathologic lesion.

Such cases have been wrongly interpreted as examples of diabetes mellitus, hyperinsulinism or dysinsulinism.

Normal oxidation of dextrose was demonstrated under all the conditions studied.

Delayed hepatic glycogenesis and impaired glycogenolysis appear to account for the disturbance in carbohydrate metabolism.

The most sensitive test of the presence of this hepatic dysfunction is the occurrence of severe hypoglycemia after restriction of carbohydrate.

Clinical cure is possible after removal of the source of the hepatitis.

SPECIFICITY OF THE AGGLUTININ REACTION FOR SHIGELLA DYSENTERIAE

I. AGGLUTINATION REACTION IN CHRONIC BACILLARY DYSENTERY; A SEROLOGIC AND BACTERIOLOGIC STUDY OF FORTY-SEVEN CASES

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The Widal test is conceded by certain investigators to be a highly important procedure in the diagnosis of infection due to Shigella dysenteriae.[1] Agglutination of any of this group of organisms by the serum of a patient is said to warrant the diagnosis of past or present dysentery or of prophylactic vaccination, provided living antigens are not used in the performance of the test.

Interpretation of the test is subject to certain well recognized sources of error. Healthy persons frequently possess normal agglutinins for S. dysenteriae.[2] The origin of these antibodies is uncertain. The responsible antigens are not known.[3] According to Arkwright [4] the agglutinins usually are not demonstrable in dilutions above 1 : 100. Gardner,[5] however, found that serum from normal persons may agglutinate strains of

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1. Davison, W. C.: A Bacteriological and Clinical Consideration of Bacillary Dysentery in Adults and Children, Medicine **1**:389-510 (Nov.) 1922. Gay, F. P., in Gay, F. P., and others: Agents of Disease and Host Resistance, Springfield, Ill., Charles C. Thomas, Publisher, 1935.

2. Ritchie, T. R.: On the Agglutination Reaction of the Bacilli of the Typhoid Dysentery Group with Normal Sera, Lancet **1**:1257-1260 (June 24) 1916.

3. Teveli, Z.: Dysenterieagglutinine, Arch. f. Kinderh. **108**:1-13, 1936.

4. Arkwright, J. A.: Agglutination, in A System of Bacteriology in Relation to Medicine, Privy Council, Medical Research Council, London, His Majesty's Stationery Office, 1931, vol. 6, chap. 12, pp. 381-423.

5. Gardner, A. D.: The Dysentery Group of Bacilli as a Whole, in A System of Bacteriology in Relation to Medicine, Privy Council, Medical Research Council, London, His Majesty's Stationery Office, 1929, vol. 4, chap. 3, pp. 161-184.

Flexner bacilli in dilutions up to 1 : 150. The titer of normal agglutinins is said to be raised by such varied stimuli as acute infectious diseases, transfusion and the exhibition of certain drugs.[6] Furthermore, it appears that the average normal agglutinin titer for Flexner bacilli varies in different localities according to the recent or the remote prevalence of bacterial dysentery of this type.[7]

Serologic diagnosis is further complicated by other factors. S-R dissociation is known to affect the specificity of the agglutination reaction. Immunization with an R antigen may produce a serum capable of agglutinating R or partially R dissociants of a number of unrelated species of bacteria.[4] This mechanism has been advanced to explain the phenomenon of para-agglutination, which is said to occur frequently in the course of intestinal infections.[8] This is characterized by the agglutination of organisms other than the known etiologic agent by the serum of persons convalescent from bacterial infection.

Although interpretation of the Widal reaction is thus subject to unavoidable error, certain of the hazards can be eliminated. The use of pure S strains minimizes group reaction. Utilization of standardized antigens prepared from these strains and treated with solution of formaldehyde further reduces the possibility of nonspecific agglutination.[9] Selection of the titer level to be considered as establishing the diagnosis remains arbitrary, however. Ritchie,[2] working in England with living antigens, concluded that definite agglutination at 1 : 125 for Flexner and at 1 : 64 for Shiga bacilli is significant. Dudgeon,[10] using antigens treated with solution of formaldehyde, held that titers for Shiga bacilli of 1 : 40 and for Flexner bacilli of 1 : 150 are diagnostic. He qualified

6. Rajchman, L., and Western, G. T.: Reports upon the Investigations in the United Kingdom of Dysentery Cases Received from the Eastern Mediterranean: II. Report upon Eight Hundred and Seventy-Eight Cases of Bacillary Enteritis, Privy Council, Medical Research Committee, Special Report Series, no. 5, London, His Majesty's Stationery Office, 1917. Martyn, R.: Wirkung der nicht spezifischen Faktoren auf den Agglutinationstiter bei Dysenterie, Monatschr. f. Kinderh. **66**:16-21, 1936.

7. Havens, L. C.: The Bacteriology of Typhoid, Salmonella, and Dysentery Infections and Carrier States, New York, Commonwealth Fund, Division of Publications, 1935.

8. Culbertson, J. T.: Acquired Immunity: The Phenomenon of Agglutination, in Gay, F. P., and others: Agents of Disease and Host Resistance, Springfield, Ill., Charles C. Thomas, Publisher, 1935.

9. Dudgeon, L. S.: The Dysentery Group of Bacilli: B. Dysenteriae (Shiga) and Schmitz's Bacillus in A System of Bacteriology in Relation to Medicine, Privy Council, Medical Research Council, London, His Majesty's Stationery Office, 1929, vol. 4, chap. 3, pp. 184-220.

10. Dudgeon, L. S., and others: Studies of Bacillary Dysentery Occurring in the British Forces in Macedonia, Medical Research Council, Special Report Series, no. 40, London, His Majesty's Stationery Office, 1919.

this, however, by the statement that there is no evidence to indicate that any standard dilution can be accepted as establishing the presence of infection by the Flexner strains. Agglutination of the Sonne bacilli at 1:25 has been considered significant.[10]

The agglutinin titer seldom reaches high levels. Dudgeon [10] found a titer of 1:480 in only 1 of 177 cases of acute Shiga dysentery. The majority were below 1:200. In only 104 of 211 cases of Flexner dysentery did the titer exceed 1:100. In only 6 cases were there agglutinins at dilutions above 1:500. The course of the agglutinin curves has been little studied except in acute infections. Patients with low titers rapidly lose their agglutinins during convalescence, provided there is no recurrence of symptoms. It is said that the agglutination reaction does not parallel the findings on culture in chronic dysentery. Glynn and Robinson [11] found that 60 per cent of the patients who were excreting Shiga bacilli gave a positive Widal reaction. On the other hand, the reaction was positive for only 20 per cent of those excreting Flexner bacilli.

TABLE 1.—*Duration of Observation*

Months	Number of Cases
6-12	4
13-24	12
25-36	12
37-48	6
49	13
	47

Delayed convalescence or relapse causes the agglutinins to disappear more slowly. Under these conditions they may remain demonstrable for a considerable period.

We have observed fluctuation of the curves for individual agglutinin titers and discrepancies between these curves and the results of repeated culture for a group of patients under prolonged observation. These findings have led us to investigate the significance of the agglutination reaction in chronic bacillary dysentery.

MATERIAL

Forty-seven patients presenting cultural or serologic evidence of infection by S. dysenteriae were studied for periods varying from six to fifty-two months. Flexner or Sonne bacilli were recovered on one or more occasions from 13 of these patients. The remaining 34 had repeatedly sterile cultures throughout the period of observation. All 47 patients exhibited chronic ulcerative lesions of the colon of the type encountered in chronic bacillary dysentery.

11. Glynn, E., and Robinson, A. L.: A Report upon 2,360 Enteritis "Convalescents" Received at Liverpool from Various Expeditionary Forces, Medical Research Committee, Special Report Series, no. 7, London, His Majesty's Stationery Office, 1917.

Two additional groups of patients were utilized for control purposes. Isolated observations, with the same technic, were made on 103 patients chosen at random from those seen in hospital, dispensary and private practice. These patients presented a variety of medical and surgical conditions.

A group in excess of 50 patients with chronic ulcerative colitis were subjected to similar repeated serologic and cultural studies, the same technic being used. The intestinal pathologic condition did not differ from that observed in the group of patients constituting the basis of this report. The duration of observation was likewise comparable.

METHODS

Plates of MacConkey's medium and eosin and methylene blue agar were inoculated directly from the rectal mucosa at proctoscopic examination. After twenty-four hours of incubation, suspicious colonies were inoculated by stab into tubes of 0.5 per cent hormone agar. Motility was tested by clouding of the semisolid medium and by hanging drop preparations of eighteen hour broth cultures. Cultures of nonmotile organisms were then transplanted by stab to semisolid sugar mediums, to peptone broth and to bromcresol purple milk. Final readings for the sugar and for the milk mediums were made after twenty-one days of incubation at 37 C. Organisms conforming to the morphologic and cultural characteristics of S. dysenteriae were tested against monovalent rabbit serum obtained from animals immunized against S stock strains of Shiga bacilli, serologic variants of the Flexner group and Sonne bacilli.

The following stock cultures were used throughout these studies:

Shiga		Obtained from the New York State Board of Health
Flexner	Karim-Kahn PB 24 Y Ledingham Logan	Obtained through Prof. E. G. D. Murray, of McGill University
	41 45	American Type Culture Collection
Sonne	E. Ledingham	Obtained through Prof. E. G. D. Murray

The first four Flexner strains and the Sonne strain were subcultures of the type organisms used by Professor Murray in his studies of the serologic variants of S. dysenteriae.[12]

Bacilli presenting the morphologic and cultural characteristics of the Salmonella group were tested against monovalent paratyphosus A and B rabbit serums.

Blood for agglutination was taken from each patient at irregular intervals throughout the period of observation. After clotting had occurred, the supernatant serum was pipetted off and used for the Widal test.

Standardized antigens prepared from the stock strains of S. dysenteriae and treated with solution of formaldehyde were used exclusively for the agglutination tests. Agar cultures were transplanted twice daily for ten subcultures. Only smooth colonies were transferred. The tenth subculture was washed off with 0.85 per cent solution of sodium chloride containing solution of formaldehyde U. S. P. (diluted 1:100) and stored at ice box temperature. The suspensions

12. Murray, E. G. D.: An Attempt at Classification of Bacillus Dysenteriae Based upon an Examination of the Agglutinating Properties of Fifty-Three Strains, J. Roy. Army M. Corps **31**:257 (Oct.-Nov.) 1918.

were all standardized to contain approximately 1,000,000,000 organisms per cubic centimeter except that of Shiga bacilli, which was standardized at 500,000,000 per cubic centimeter. The agglutinability of the antigens was then measured in homologous monovalent rabbit serum of known titer. A test was made for spontaneous agglutination, at the time each Widal test was made, by suspension in 0.85 per cent solution of sodium chloride. Standard agglutination tubes were used for all Widal tests. Equal parts of serum diluted with 0.85 per cent solution of sodium chloride and suspension of standardized antigen were added to each tube. The antigen serum mixtures were kept in the water bath at 55 C. for four hours and then at ice box temperature over night before readings were made. In each instance the full titer of the patient's serum was measured as shown by definite though incomplete agglutination. The last tube showing definite clumping to the unaided eye was considered the end point. The upper limits of the agglutinin titers as determined by this method have been used throughout this study.

FINDINGS FOR CONTROL GROUPS

Serum from 6 of the 103 patients chosen at random agglutinated some strains of S. dysenteriae at a dilution of 1 : 160. One sample

TABLE 2.—*Agglutinin Titer in Thirteen Cases in Which Cultures Were Positive*

Titer of Serum	Number of Cases		
	Shiga Agglutinins	Sonne Agglutinins	Flexner Agglutinins
1:40	4	..	..
1:80	1	..	..
1:160	1	2	3
1:320	..	2	8
1:640	..	..	1

agglutinated at 1 : 320. Four of these 7 patients gave a history of chronic or recurrent diarrhea. One was a healthy laboratory technician who was engaged in these studies, 1 had intestinal amebiasis and 1 had subacute bacterial endocarditis. Positive cultures were obtained for 2 others who gave a negative reaction to the Widal test.

The serum of control patients with chronic ulcerative colitis without exception gave repeatedly negative agglutination reactions and sterile culture.

FINDINGS FOR PATIENTS WITH POSITIVE CULTURES

In 13 of the 47 cases S. dysenteriae was obtained on culture. Flexner bacilli were recovered in 11 and Sonne bacilli in 2 cases. No case of Shiga infection was found. The maximum agglutinin titers observed for these patients were not high and were subject to marked variation. Only 1 patient showed agglutination at a dilution of 1 : 640. Agglutinins for the Flexner strains were most commonly encountered and tended to reach the highest levels. In only 1 instance were agglutinins for the Shiga bacillus observed at a dilution of 1 : 160.

The agglutinin curves in certain illustrative cases are discussed in detail and presented in graphic form.

The serum in 6 of the 13 cases in which culture was positive agglutinated the Shiga bacillus at dilutions of 1 : 40 or higher. In 5 of these 6 cases Flexner bacilli were recovered, and in 1 case a Sonne bacillus was obtained on culture. Partial agglutination at a dilution of 1 : 160 was the highest titer observed. This coincided with like titers for Flexner and for Sonne bacilli and with the isolation of a Flexner bacillus in case 12 (chart 1). This patient was studied for forty-two months. Flexner bacilli were recovered twelve times. After the initial agglutination reaction, the Shiga agglutinins disappeared and were not again demonstrable in five subsequent tests.

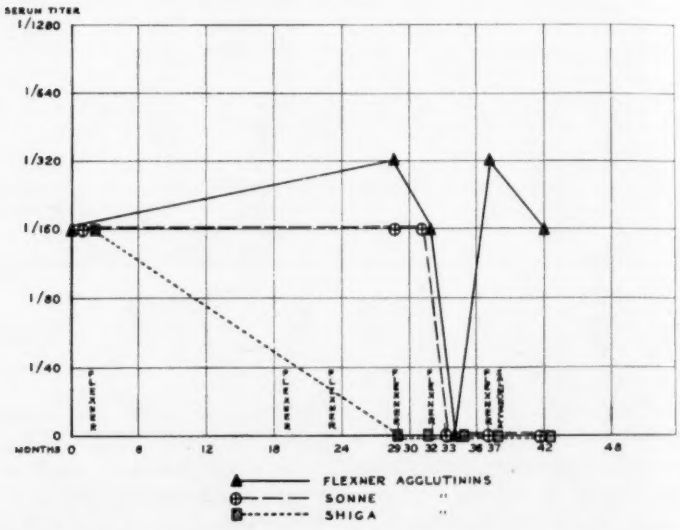

Chart 1 (case 12).—A total of twenty-two cultures were made. Flexner bacilli were present in twelve cultures.

Serum from 4 patients agglutinated the Sonne bacillus. In 2 cases the titer reached 1 : 320 and in 2 1 : 160. Flexner bacilli were recovered repeatedly from all 4 patients. Neither of the 2 patients from whom Sonne bacilli were isolated possessed demonstrable agglutinins for these organisms, despite repeated testing. However, only one positive culture was obtained for each.

Case 12 (chart 1).—This patient carried a heavy Flexner infection throughout the forty-two months of observation. These organisms were recovered on twelve of twenty-two attempts. Serum from this patient agglutinated Sonne bacilli at a dilution of 1 : 160 at the initial determination, again at twenty-nine months and again at thirty-two months. Immediately thereafter the titer fell to zero and remained there.

CASE 8 (chart 2).—In this case no Sonne agglutinins were demonstrable at four determinations in the course of the first thirty-five months. Four months later, after Flexner bacilli had been recovered on three occasions, the titer for Some bacilli rose to 1:320, only to fall promptly to zero, rising again subsequently to 1:160 at two successive determinations.

Flexner agglutinins were invariably demonstrable at some time in all cases in which these organisms were recovered. The titer curve frequently showed marked and unaccountable fluctuation. Agglutination at a dilution of 1:640 was observed only once (case 2; chart 3). This patient was studied for fifty months. Flexner bacilli were recovered twice in nineteen cultures. At the outset no agglutinins for dysentery bacilli were demonstrable. Coinciding with the first positive culture, Flexner bacilli were agglutinated at a titer of 1:640. Four months later the titer fell to 1:40, followed after two months by a rise to 1:320. Another immediate fall, this time to zero, was followed by a third rise, reaching 1:320 at the last observation. It is of interest that this lightly infected patient gave the highest agglutinin titer of the group who showed positive cultures.

In case 8 (chart 2) the initial Flexner titer of 1:320 dropped to zero for two determinations prior to the recovery of Flexner bacilli, when agglutinins were again present at a dilution of 1:160. Four months later no Flexner agglutinins were demonstrable, although Sonne bacilli were agglutinated at a titer of 1:320. A second, sustained rise of the Flexner titer to 1:160 and 1:320 coincided with the isolation of an unidentified salmonella and Bacillus alcaligenes. Flexner bacilli were recovered three times in the course of thirty-four cultures in fifty-one months. In case 12 (chart 1) there was a drop in titer from 1:320 to zero, followed by an abrupt secondary rise to 1:320, within a period of eight months. This patient was heavily infected, yielding Flexner bacilli in twelve of twenty-two cultures throughout a period of forty-two months.

CASE 1.—This patient was studied for forty-three months. At the initial observation, Flexner agglutinins were present at a titer of 1:160. No Shiga or Sonne agglutinins were demonstrable. Thirty months later Flexner bacilli were isolated for the first time. The agglutination remained unchanged. In the course of the ensuing thirteen months Flexner bacilli were isolated on twelve different occasions. At thirty-two months the agglutinin titer for both Flexner and Sonne strains rose to 1:320 and for Shiga strains to 1:80. The Sonne titer remained unchanged at thirty-six, thirty-nine and forty-three months. Shiga agglutinins were absent at thirty-six months and did not reappear. The Flexner titer, however, fell to 1:160 at thirty-six and at thirty-nine months, rising again to 1:320 at the final determination. In this case, therefore, there was an abrupt and sustained rise of heterologous agglutinins immediately after the first positive culture was obtained. On two occasions subsequently the heterologous agglutinin titer exceeded the homologous titer.

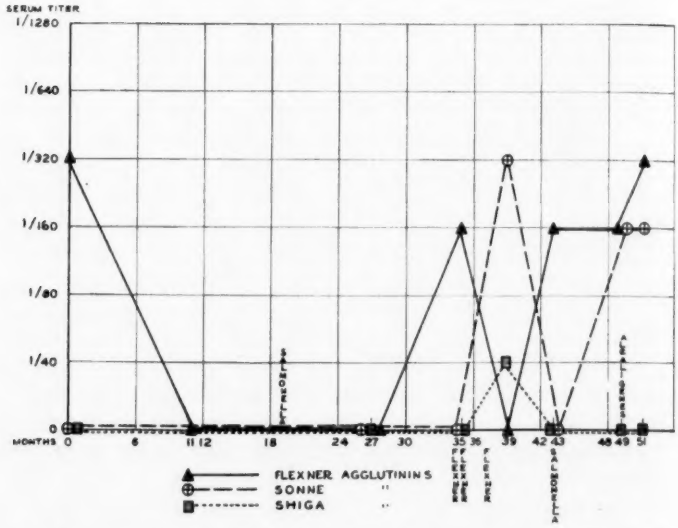

Chart 2 (case 8).—A total of thirty-four cultures were made. Flexner bacilli were present in three.

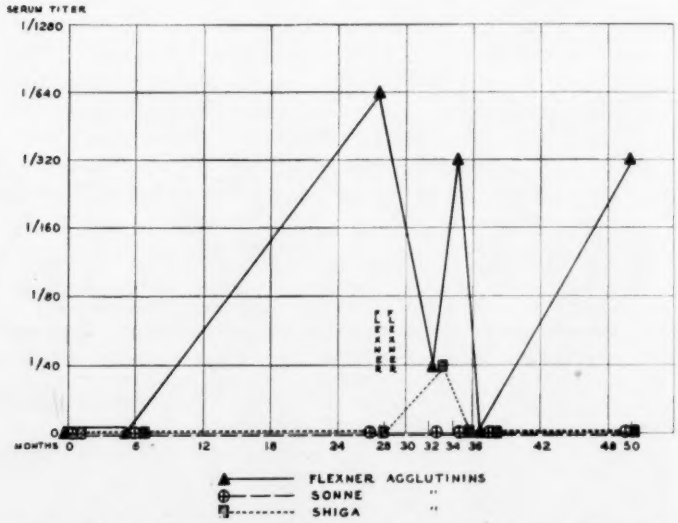

Chart 3 (case 2).—A total of nineteen cultures were made. Flexner bacilli were present in two.

CASE 3.—This patient was studied inconstantly for forty-nine months. Flexner bacilli were recovered twice at the outset. Nine subsequent cultures were sterile. No agglutinins for any of the strains of S. dysenteriae were demonstrable when the two positive cultures were obtained. Three months later the Flexner titer rose to 1:160, only to fall again to zero at six months and at fourteen months. Flexner agglutinins were again demonstrable at a dilution of 1:160 at forty-nine months. No agglutinins for Shiga or Sonne bacilli were found at any time. In this case, therefore, there was a transitory low homologous agglutinin titer shortly after proof of the infection was obtained. Forty-six months later an equal secondary rise was observed, unaccompanied by cultural evidence of infection by S. dysenteriae.

FINDINGS FOR PATIENTS WITH STERILE CULTURES

In 34 cases in which cultures were consistently sterile, agglutinins for S. dysenteriae were found at titers usually considered as establishing the diagnosis. High titer reactions were more common for this group than for the group of patients for whom cultures were positive. Moreover, the highest titers observed for Shiga, Sonne and Flexner agglutinins were found for the group of patients with sterile cultures. The agglutinin curves exhibited similar marked fluctuations.

TABLE 3.—*Agglutinin Titer in Thirty-Four Cases in Which Cultures Were Sterile*

Titer of Serum	Number of Cases		
	Shiga Agglutinins	Sonne Agglutinins	Flexner Agglutinins
1:40	9	..	..
1:80	5	..	..
1:160	5	14	5
1:320	1	9	10
1:640	..	6	14
1:1280	..	..	1

In 20 of the 34 cases there was agglutination of Shiga bacilli at dilutions of 1:40 or higher. In 1 instance the titer reached 1:320, accompanying a titer of 1:160 for Flexner bacilli. The serum of 5 patients agglutinated Shiga bacilli at a dilution of 1:160.

CASE 18 (chart 4).—This patient was studied for twenty-six months. Seventeen sterile cultures were obtained. No Shiga agglutinins were demonstrable at the initial determination. In the following fourteen months the titer rose to 1:60 and fell again gradually to zero. A secondary rise to 1:80 at sixteen months was followed by disappearance of these antibodies. Throughout the period of observation, agglutinins for Flexner bacilli remained at a high titer, accompanied by a markedly fluctuating curve for Sonne bacilli.

CASE 31 (chart 5).—This patient was under observation for twenty-five months. Nineteen sterile cultures were obtained. An initial titer of 1:40 for Shiga bacilli fell to zero at six months, followed by a rise to 1:160 at seven months. Three months later Shiga agglutinins were absent, only to reappear at a titer of 1:80 at twelve months. After this observation they disappeared permanently. In this case likewise there was a high titer curve for both Flexner and Sonne bacilli.

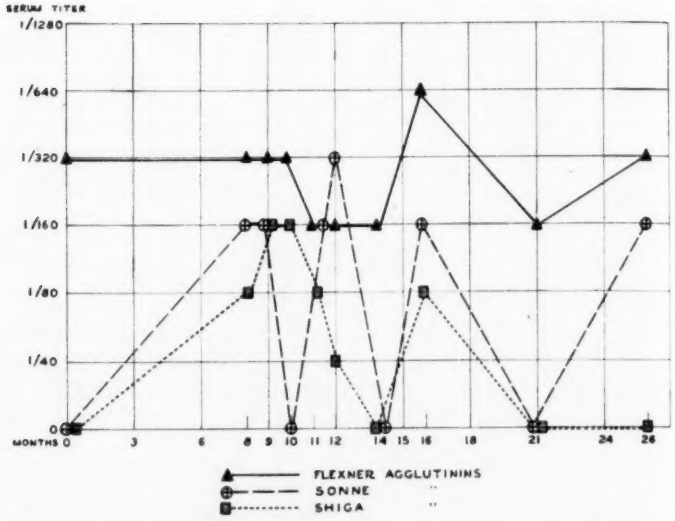

Chart 4 (case 18).—A total of seventeen cultures were made.

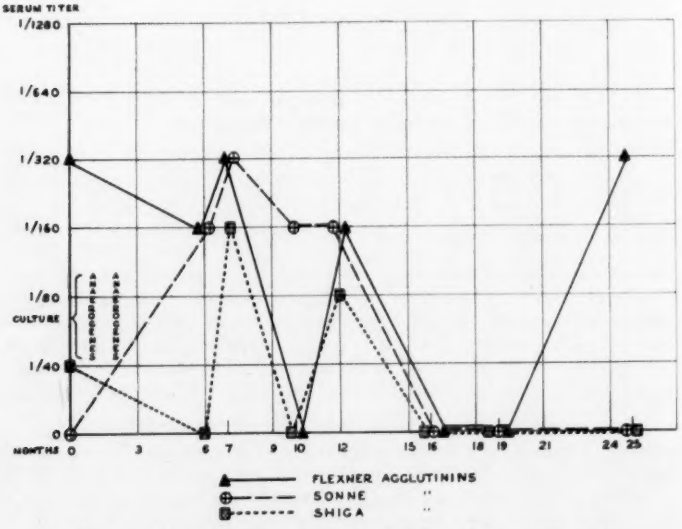

Chart 5 (case 31).—A total of nineteen cultures were made.

The curves for the other patients exhibiting Shiga agglutinins presented essentially the same variations. None of the serums agglutinated the Shiga bacillus at a higher titer than it did the Flexner or the Sonne strains. A like titer for all three organisms was observed in 3 cases.

In 29 cases there was agglutination of Sonne bacilli at dilutions of 1:160 or above, in 6 of these cases reaching a titer of 1:640. The serum of 5 patients contained agglutinins for Sonne bacilli at a higher dilution than for either Flexner or Shiga bacilli. In general the Sonne agglutinin curves exhibited similar marked variations of titer.

CASE 41 (chart 6).—This patient was observed for twenty-six months, in the course of which thirty-nine sterile cultures were obtained. Throughout this

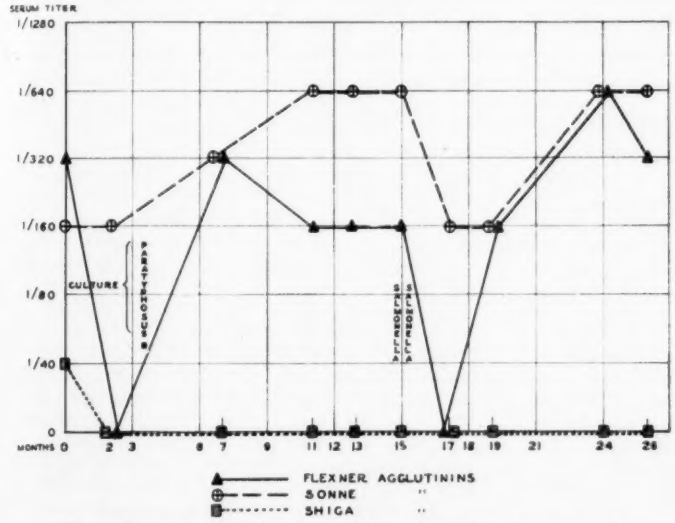

Chart 6 (case 41).—A total of thirty-nine cultures were made

period Sonne agglutinins were present at significant dilutions. The first two determinations revealed a titer of 1:160. This rose at seven months to 1:320 and at eleven months to 1:640, where it remained for two subsequent determinations. This was followed by a fall to 1:160 and subsequent rise to 1:640. In this case also there was an irregular Flexner agglutinin curve, which on one occasion reached a titer of 1:640.

CASE 31 (chart 5).—In this case there was a relatively smooth curve for Sonne agglutinins which did not parallel the curves for Shiga or Flexner agglutinins. The Sonne titer rose from zero to 1:160 at six months and to 1:320 at seven months. It then fell to 1:160 at ten and at twelve months and to zero at sixteen months.

Extreme fluctuations, however, were observed. In case 18 (chart 4) there was consistent agglutination of Flexner bacilli at dilutions varying

from 1 : 160 to 1 : 640. This was accompanied by a markedly fluctuating curve for both Sonne and Shiga bacilli. The curve for the Sonne agglutinins did not parallel the curves for the other two organisms. Starting at zero, Sonne agglutinins rose to 1 : 160 at eight and at nine months and returned to zero at ten months. At eleven months they again rose to 1 : 160 and at twelve months to 1 : 320, followed by a drop to zero at fourteen months. At sixteen months the Sonne bacilli were again agglutinated at a titer of 1 : 160, but a negative reaction was obtained at twenty-one months, followed by another rise at twenty-six months. Seventeen cultures were sterile for S. dysenteriae.

In 30 of the 34 cases there was agglutination of Flexner bacilli at dilutions of 1 : 160 or higher. High titers were more common for Flexner strains than for either Shiga or Sonne strains. In 1 instance the Flexner titer reached 1 : 1,280. The curves of the Flexner agglutinins showed irregularities similar to those of the curves for the other organisms and did not parallel the curves of the Shiga and the Sonne agglutinins.

Case 18 (chart 4).—This patient presented a Flexner titer of 1 : 320 on four occasions in the first ten months. At eleven, twelve and fourteen months the curve fell to 1 : 160. This was followed by a rise to 1 : 640 at sixteen months, another fall to 1 : 160 at twenty-one months and a further rise to 1 : 320 at twenty-six months. The Shiga and the Sonne agglutinins varied markedly during the period of observation.

Case 31 (chart 5).—In this case there was agglutination of Flexner bacilli at a dilution of 1 : 320 at the initial determination. The titer fell to 1 : 160 at six months and rose again to 1 : 320 at seven months. Three months later Flexner agglutinins were not demonstrable. At twelve months agglutinins were present at a dilution of 1 : 160. The curve then again fell to zero at sixteen and at nineteen months, followed by a rise to 1 : 320 at the last determination.

Case 41 (chart 6).—This patient likewise revealed a fluctuating titer for Flexner bacilli in the course of ten determinations over a period of twenty-six months. Starting at 1 : 320, the curve fell to zero at two months. After the isolation of a salmonella agglutinating at low titer in paratyphosus B serum, Flexner agglutinins again rose to 1 : 320. The titer remained at 1 : 160 at eleven, thirteen and fifteen months, again falling to zero at seventeen months. The curve then rose again to 1 : 160 at ninteen months and to 1 : 640 at twenty-four months, thereafter falling to 1 : 320 at the final determination. This patient presented a consistently higher titer for Sonne agglutinins.

Case 45.—This patient presented the highest titer which we have seen. The titer for agglutinins for Flexner bacilli reached 1 : 1,280, and that for Sonne bacilli reached 1 : 640. Cultures of the stool in another institution just prior to this finding were sterile, and five cultures of rectal mucosa made during the ensuing twelve months also failed to reveal S. dysenteriae. Death occurred at the end of this period. Postmortem cultures of samples from the colon and the ileum were sterile.

CASE 15.—This patient was under observation for seventeen months, in the course of which fifteen sterile cultures were obtained. At the initial determination Sonne agglutinins were present at a dilution of 1:640. Coincidentally a salmonella agglutinating at a titer of 1:320 in paratyphosus B serum was isolated. At three and at eight months no dysentery agglutinins were demonstrable. At sixteen months Sonne and Flexner agglutinins were present at a dilution of 1:160. One month later the Flexner titer remained unchanged, and Sonne agglutinins were absent.

CASE 17.—This patient was under observation for twenty-four months. Sixteen sterile cultures were obtained. No dysentery agglutinins were demonstrable at the initial determination. Twelve months later Shiga bacilli were agglutinated at a titer of 1:320 and Flexner bacilli at 1:160. At twenty-four months both Shiga and Flexner agglutinins were absent. However, Sonne agglutinins, previously not demonstrable, were obtained at a titer of 1:320.

CASE 21.—This patient was under observation for sixteen months. Eleven sterile cultures were obtained. The initial Flexner titer was 1:160; the titer rose to 1:320 at three and at five months and to 1:640 at seven months, where it remained constant for three subsequent determinations at eleven, twelve and sixteen months. Sonne agglutinins were present at a titer of 1:320 at the first examination; the titer rose to 1:640 at three months, fell to 1:320 at five months and rose again to 1:640 at seven months. At eleven months the titer dropped again to 1:320 and at twelve months to 1:160. At the final determination it was again at 1:640. Agglutinins for Shiga bacilli were present at a titer of 1:80 at the first examination, the titer rising to 1:160 at three months. There was no agglutination at five, seven and eleven months. At twelve months the titer had risen to 1:80, and agglutination was again absent at the last determination.

CASE 27.—This patient was under observation for twenty-two months. Twenty-five sterile cultures were obtained. No dysentery agglutinins were demonstrable at the initial determination. At five months a Flexner titer of 1:320 was found, falling to 1:160 at nine months and rising to 1:640 at thirteen months. This was followed by a fall to 1:160 at sixteen months and a further rise to 1:320 at eighteen months and to 1:640 at twenty-two months. Sonne agglutinins were present at a titer of 1:320 at five months, the titer falling to 1:160 at nine and at thirteen months. There was no agglutination at sixteen and at eighteen months, but the titer was again at 1:160 at the final observation. Shiga agglutinins were absent throughout except at five months, when a titer of 1:80 was found.

CASE 35—This patient was under observation for fifty-two months. Thirty-one sterile cultures were obtained. Three determinations in the first thirteen months failed to demonstrate agglutinins for dysentery bacilli. At twenty-five and at thirty-five months Flexner agglutinins reached a titer of 1:160. This rose to 1:320 at forty-two months. A fall to 1:160 at forty-five months was followed by a rise to 1:640 at fifty-two months. Sonne agglutinins were absent throughout except for the final determination, when a titer of 1:160 was found. Shiga bacilli were not agglutinated at any time.

COMMENT

The data obtained in these studies suggest the need for caution in the interpretation of the agglutination reaction. High serum titers do

not regularly accompany chronic infections due to S. dysenteriae. In the course of a heavy long-continued Flexner infection, the patient's serum may contain agglutinins at equal titer for the Shiga, the Sonne and the Flexner bacillus. Sonne organisms may be agglutinated to a higher titer than Flexner organisms in the course of proved infection. Agglutinins for the Flexner strains may maintain a relatively constant level, or they may fluctuate markedly, often disappearing temporarily in the course of proved homologous infection.

It has not been possible to correlate the variations in agglutinin titer with the associated bacterial flora, with the clinical condition of the patient or with the condition of the lower portion of the colon as seen at proctoscopy. Moreover the height of the agglutinin titer does not appear to be a measure of the chronicity or of the intensity of the infection. Only two positive cultures for S. dysenteriae were obtained for the patient with the highest agglutinin titer. Of the 9 patients presenting agglutinins at dilutions of 1 : 320 or higher, only 3 yielded more than 6 positive cultures.

The predominance of higher titers for all three of the strains of S. dysenteriae in the cases in which culture was sterile is striking. Not even the most heavily infected patients possessed agglutinins at levels frequently found for patients who repeatedly yielded sterile cultures. As was the case in the group of patients with proved infection, the agglutinin curves were subject to marked and irregular fluctuation from zero to relatively high levels in the course of a few months, or a consistently rising titer was encountered. Frequently there was a complete lack of parallelism between the individual agglutinin curves for Shiga, Sonne and Flexner bacilli for the same patient. Again, it has not been possible to correlate these findings with demonstrable changes in the clinical condition, the associated bacterial flora or the appearance of the mucosa of the lower portion of the colon.

For both the patients who showed positive cultures and those who showed sterile cultures, the Flexner agglutinins were demonstrable at higher dilutions than the Sonne or the Shiga agglutinins. The Sonne agglutinins occupied an intermediate position. Agglutinins for Shiga bacilli were rarely encountered at dilutions of 1 : 160 or higher.

Certain of these findings raise a question as to the specificity of the Widal reaction in chronic dysentery. It is more difficult to concede specificity in the face of lower average agglutinin titers when culture is positive than when it is sterile. It is difficult to explain the marked variations in the curves observed for both groups of patients. The association of Sonne agglutinins at equal or at higher titers than those for Flexner bacilli in the course of a heavy Flexner infection is contrary to expectation.

It is unlikely that normal agglutinins for S. dysenteriae are responsible for these facts. The findings for the two control groups strongly suggest that normal agglutinins are not common in persons living in the city of New York and that they do not ordinarily reach a high titer. It is recognized, however, that isolated observations cannot be completely satisfactory, especially in view of the variations in titer observed in the cases under discussion.

The anamnestic reaction may be advanced to explain the persistence of agglutinins in the cases in which cultures were sterile. Yet it is

TABLE 4.—*Associated Bacteria in Thirteen Cases in Which Cultures for S. Dysenteriae Were Positive*

Bacteria Recovered	Number of Cases
S. dysenteriae Flexner	11
S. dysenteriae Sonne	2
Salmonella, unidentified	5
Paratyphosus B	1
Pyocyaneus	2
B. coli anaerogenes	1
B. alcalescens	1
B. faecalis alcaligenes	2
Beta hemolytic streptococci	4
Nonhemolytic streptococci	2

TABLE 5.—*Associated Bacteria in Thirty-Four Cases in Which Cultures for S. Dysenteriae Were Sterile*

Bacteria Recovered	Number of Cases
Salmonella, unidentified	16
Paratyphosus B	5
Paratyphosus A	1
B. morgani 1	4
B. coli anaerogenes	4
B. alcaligenes	2
B. proteus	5
B. fluorescens	1
B. pyocyaneus	1
Beta hemolytic streptococci	7
Nonhemolytic streptococci	7

unlikely that such a mechanism should frequently give rise to agglutinins for S. dysenteriae at higher titers than those observed in cases of proved homologous infection.

It is recognized that sterile cultures do not constitute proof that an organism is absent. The Flexner bacilli especially are notoriously difficult to recover. The mediums used in these studies, the number of cultures taken, the technic of culture and the duration of the period of observation indicate that if S. dysenteriae was present, the infection must have been light.

The possibility that the agglutinins for S. dysenteriae may be produced as a nonspecific response to infection of the colon by other types of bacteria remains to be considered. Heterologous R agglutination was

guarded against throughout these studies by the use of antigens, treated with solution of formaldehyde, prepared from S strains of known agglutinability in homologous and heterologous antidysentery rabbit serums.

The possibility of para-agglutination [8] cannot be definitely eliminated. The cultural studies of these patients included repeated search for S. dysenteriae and for other potential pathogens which might play a role in the production of the intestinal pathologic condition. Exclusive of Escherichia coli, various members of the salmonella group were recovered more frequently than any other species of bacteria (tables 4 and 5). These organisms were isolated in 28 of the 47 cases. Although this constitutes a high rate of incidence, it cannot be interpreted to explain the production of nonspecific agglutinins. Furthermore, the agglutination reactions of these strains of Salmonella in serum of patients and in the monovalent dysentery rabbit serum failed to indicate any cross immunologic relationship between these organisms and S. dysenteriae. It is impossible to confirm or to refute the potential role of para-agglutination in these cases at present.

The relation between the production of S. dysenteriae agglutinins and heterologous infection will be detailed in a subsequent communication.

SUMMARY

Prolonged serologic and cultural studies indicate the necessity for cautious interpretation of the agglutination reaction in cases of chronic inflammatory disease of the colon. We have repeatedly found agglutinins for S. dysenteriae present at titers commonly considered to establish the diagnosis unaccompanied by cultural evidence of homologous infection. Conversely, no agglutination reactions have been observed in cases of proved infection. Marked and unaccountable variations of agglutinin titer are the rule in the course of repeated determinations. It is a striking fact that the majority of the serums which gave a high titer were obtained from patients who consistently showed sterile culture for S. dysenteriae. These observations suggest that agglutinins for S. dysenteriae may develop in response to nonspecific heterologous stimuli.

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RELATION OF AGE TO RENAL PRESSOR SUBSTANCE

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Elevation of the blood pressure is rare in children, occurs occasionally in young adults and appears frequently in elderly persons. Any satisfactory hypothesis of the mechanism of hypertension must necessarily explain the striking variations in the frequency of this disorder at different ages. In the course of an investigation of the possible relation of the renal pressor substance (the renin of Tigerstedt and Bergman [1]) to certain types of experimental hypertension, we have compared the sensitivity of rats of different ages to this agent. Studies have also been made of the amount of pressor substance in the kidneys of such rats.

METHOD

Fresh kidneys of hogs were obtained from the slaughter house. The renal cortex was separated from the medulla, passed through a meat grinder and then ground to a fine paste with carborundum. Ninety-five per cent alcohol was then added, in a ratio of 9 cc. to 1 Gm. of cortical tissue. The mixture was allowed to stand in the ice box for twenty-four hours or longer and then centrifuged while still cold. After the supernatant alcohol had been poured off, the residue was treated with ether and then spread out on flat plates and dried under a fan. The dry powder was ground in a mortar with 0.5 per cent sodium bicarbonate at a temperature of 40 to 45 C. After centrifugation the supernatant fluid was saved, and the residue was twice reextracted, the total amount of bicarbonate solution added being equal to 2 cc. per gram of original renal cortex. The supernatant fluids obtained by centrifugation after the extractions were mixed and kept in the ice box until the time of injection.

Rats of known age were obtained either from the Wistar Institute or locally.[2] The sensitivity of these rats to renal extract was determined as follows: Pentobarbital sodium (3 or 4 mg. per hundred grams of body weight) was administered intraperitoneally. The abdomen was then opened, and a needle (22 to 16 gage) was tied into the lower abdominal aorta. By means of a three way stopcock this needle could be connected either to a small bore mercury manometer for direct reading of the aortic blood pressure or to a syringe for the injection

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This investigation was aided by a grant from the Josiah Macy Jr. Foundation.

1. Tigerstedt, R., and Bergman, P. G.: Niere und Kreislauf, Skandinav. Arch. f. Physiol. **8**:223, 1898.

2. Dr. Karl Mason, of the department of anatomy, supplied some of the rats used in this work.

of solution into the aorta. A small amount of solution of heparin was injected in order to prevent clotting. The amount of renal extract given was calculated according to the following formula:

$$\frac{(\text{Body weight in grams})^{2/3} \times 2}{100} = \text{cubic centimeters to be injected}^{3}$$

It was thought that the body surface, which is proportional to the two-thirds power of the weight, would be a more reliable index of dosage than the body weight. It should be noted that the smaller rats received considerably larger doses in proportion to the body weight than did the larger rats. After the injections the blood pressure was read at intervals of fifteen seconds for a period of thirty minutes.

The results obtained for a given rat were discarded when (*a*) the initial mean arterial blood pressure was below 90 mm. of mercury, (*b*) the animal died within the thirty minute period after receiving the injection or (*c*) a marked decline in blood pressure (below the initial level) occurred before the end of the thirty minute period. For purposes of comparison the values obtained for 3 to 6 animals in each age group were averaged.

Prior to the insertion of the needle into the aorta, the kidneys of the rat were removed, weighed, ground and treated with 9 volumes of 95 per cent alcohol. The kidneys of the rats of a given age group were then mixed, and an extract was prepared by the same technic as that used for hog kidneys. This extract was then tested on other rats, according to the technic just described, female rats approximately 4 months of age being used.

RESULTS

In the first experiment three groups of female rats were studied, their ages being approximately 10 weeks, 1 year and 2 years, respectively. The youngest were decidedly less responsive than the two groups of older rats, the 1 year old animals being slightly more sensitive than the 2 year olds.

In the second experiment three groups of male rats were used. Again the youngest rats displayed the smallest rise in blood pressure, but in this series the oldest rats (2 years) were somewhat more sensitive than the animals of intermediate (1 year) age.

A third experiment was then carried out on rats of both sexes that were 6 weeks, 6 months, 1 year and 2½ years old, respectively. The results of this experiment, which are shown in chart 1, indicated again that the youngest rats were the least sensitive. The senile (2½ years) rats gave the greatest rises in blood pressure. Consistent differences between the rises in blood pressure obtained in the two intermediate age groups (6 months and 1 year) were not observed, the values for both of these groups falling between those for the immature (6 weeks) and those for the senile (2½ years) animals.

The data were then analyzed from the standpoint of the sex of the rats, but no consistent differences between the pressor responses of

3. Thus a rat weighing 100 Gm. would receive 0.43 cc.; one weighing 200 Gm., 0.68 cc., etc.

males and those of females of a given age were noted. Accordingly, all the figures for animals of the same age groups, regardless of sex, were combined, and the averages were computed. The curves for the animals of the intermediate groups (6 months, 1 year and 2 years) crossed each other several times (chart 2) and displayed no consistent differences. However, the youngest rats (6 to 10 weeks) showed the least response and the oldest rats (2½ years) the greatest response (chart 2). The differences observed could not be ascribed to variations in the initial blood pressure levels, for these showed no consistent relation to the age of the animals.

In order to determine whether the differences in sensitivity were due to a general increase in sensitivity to pressor agents with increasing age, the animals used in the third experiment were given injections of 1:2,000,000 solution of epinephrine hydrochloride, the doses being calculated in the same way as when renal extract was used. Consistent differences in the response to epinephrine of the animals of different ages were not observed, the general tendency being for the older animals to be slightly less sensitive than the younger ones (chart 1).

The data were next analyzed from the standpoint of the body weight. No consistent relation between this factor and the sensitivity of the animal was observed. Thus, for the experiment recorded in chart 1, the 6 month old males happened to be larger than any of the other animals. Their average body weight was 415 Gm., while the averages for the 2½ year old animals were 366 Gm. for males and 275 Gm. for females. However, these senile animals displayed a considerably greater rise in blood pressure than did the larger, 6 month old rats. Furthermore, if the increased response of the senile rats and the diminished sensitivity of the immature rats were due mainly to difference in size, one would expect males to show greater responses than females of the same age. Such was not the case. The size of a rat is evidently less important than its age in determining its sensitivity to renal pressor substance.

The pressor effects of renal extracts made from rats of different ages were compared by injecting the extracts into other rats. Two methods of comparison were used:

1. Two rats were given injections of the extracts of the kidneys of rats of each age group, the blood pressure being followed for thirty minutes, as in previous experiments. The greatest rise in blood pressure was obtained from the extract of the kidneys of the youngest rats, the least rise from that of the oldest rats and the intermediate response from that of rats of intermediate age (chart 3). No significant difference was found between the pressor effect of extract of kidneys of male and that of female rats of the same age.

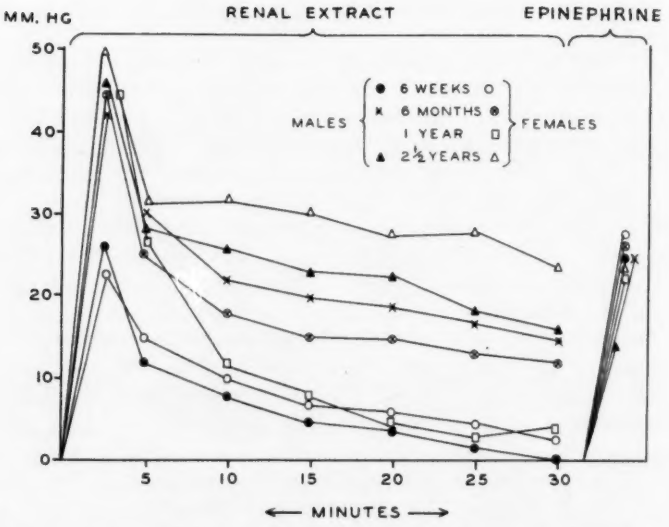

Chart 1.—An example of a day's experiment. Each curve represents the average blood pressure response of 2 to 5 rats that were given renal extract, as explained in the text. It will be seen that the young rats are the least sensitive and the senile ones the most sensitive and that the curves for the groups of rats of intermediate ages fall between the curves for these two groups. There is overlapping of the curves for the intermediate groups. There is no consistent difference with regard to sex. The column of figures to the left shows the rise in mean arterial blood pressure after the injection of renal extract.

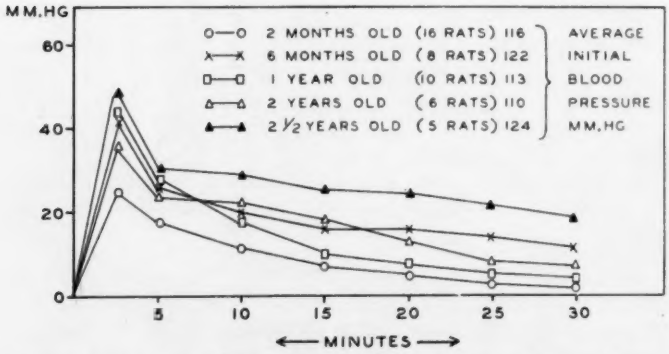

Chart 2.—A composite chart of the results of all three experiments. As shown in chart 1, the old rats are the most sensitive and the young rats the least sensitive, and there is again some overlapping of the curves for the intermediate groups, which fall between those for the oldest and the youngest rats. The column of figures to the left shows the rise in mean arterial blood pressure after the injection of renal extract.

2. Comparisons were made by giving a group of rats alternate injections of the extract of kidneys of younger and that of older rats. Because of the marked decrease in response to successive doses, the effect of the injection of a given extract was compared with the average effect of the preceding and of the succeeding injection of the extract to be compared with it. Twenty such comparisons were made. In 15 instances the extract of the kidneys from the younger rats gave a greater pressor effect than did that from the older rats. In no instance was a greater effect obtained from "old" kidney than from "young" kidney. Five comparisons yielded inconclusive results; i. e., the pressor responses did not differ more than 5 mm. Four comparisons were

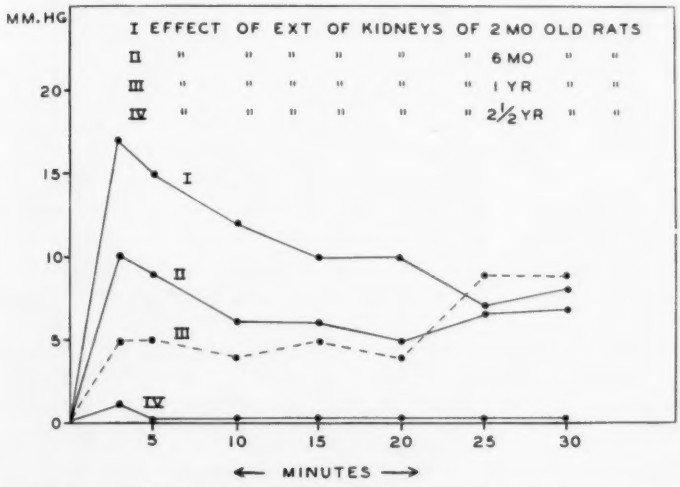

Chart 3.—This chart represents the average rises in blood pressure produced by renal extracts of rats of various ages in 4 month old female rats. It shows the oldest rats to have the least pressor substance and the youngest rats the most, with the curves for the intermediate rats falling between in their proper order. The column of figures to the left shows the rise in mean arterial blood pressure after the injection of renal extract.

made of renal extract obtained from the kidneys of male and that of female rats of the same age. In each instance no significant difference was found.

These experiments indicate clearly that in rats the amount of renin in the kidneys diminishes with advancing age.[4]

4. Since this report was written we have found that the kidneys of calves contain more renin than those of adult cattle.

The data which have been presented show clearly that with advancing age the amount of pressor substance (per unit of renal weight) in the kidneys diminishes progressively. The data also show that senile rats are more responsive and immature rats less responsive to a given dose of renin than are rats of intermediate ages.[5] There seems to be relatively little difference in the sensitivity of groups of mature rats of different ages short of senility, but senile rats are definitely more sensitive than mature adult animals.

Whether renal pressor substance (renin) is related in any way to the tendency of elderly persons to show hypertension is not known. If such a relation does exist, it appears to be concerned with a disturbance in the capacity of the older organism to destroy, neutralize, excrete or otherwise overcome the effects of renin rather than with increased formation of this substance by the kidney.

SUMMARY

Extracts containing renal pressor substance (renin) were administered to rats of various ages in doses proportional to the body surface. The youngest rats (6 to 10 weeks) showed the least rise in blood pressure, the oldest (2½ years) displayed the greatest pressor effect and intermediate responses were displayed by rats of intermediate age (6 months to 2 years). On the other hand, the youngest rats had the most pressor substance in their own kidneys, and the oldest rats had the least.

The greater sensitivity of the oldest animals to renal pressor substance did not appear to be dependent on a general increase in reactivity to all pressor agents, for the administration of epinephrine produced as great a rise in blood pressure in the young as it did in the older animals.

The experiments suggest a possible relation between the increased sensitivity of senile rats to renal pressor substance and the tendency of elderly persons to show hypertension. However, it is concluded that no convincing evidence of such a relation exists at present.

5. This statement applies when doses are given according to body surface. If doses are given according to body weight, the difference between the sensitivity of young and that of old rats is still greater.

RELATION OF RENAL PRESSOR SUBSTANCE TO HYPERTENSION OF HYDRO-NEPHROTIC RATS

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In the course of investigations concerning the renal pressor substance (Tigerstedt's renin) we have encountered a number of rats with spontaneous hydronephrosis. Such animals are usually found to have an elevation of blood pressure. The following investigations were undertaken to obtain information concerning the mechanism of the rise in blood pressure displayed by these animals:

METHODS

After anesthesia had been induced by the intraperitoneal injection of pentobarbital sodium, the blood pressure was measured by cannulation of the abdominal aorta with a needle attached to a small bore manometer, heparin being used to prevent clotting. The renal pressor substance was prepared from pig kidneys by precipitation with alcohol and extraction with dilute solution of sodium bicarbonate according to the technic described by Grossman.[1]

Observations of two different types were made. In one series of experiments the sensitivity of hydronephrotic rats to renal pressor substance was compared with that of normal animals of the same size and of approximately the same age. For this purpose all the animals received doses calculated according to the following formula:

$$\frac{\text{Body weight in grams}^{2/3} \times 2}{100} = \text{cubic centimeters to be injected}$$

After this the blood pressure was read from the manometer at frequent intervals for thirty minutes. In a second series of experiments the pressor effects of hydronephrotic and of normal kidneys of rats were compared by making saline extracts and injecting these into normal rats. For this purpose the kidneys were ground with carborundum, a measured amount of 0.9 per cent solution of sodium

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* Fellow of the Commission for Relief in Belgium of the Educational Foundation, Inc.

1. Grossman, E. B.: A Note on the Preparation of Extracts of the Renal Pressor Substance, Proc. Soc. Exper. Biol. & Med., to be published.

chloride was added and the mixture was ground further and then centrifuged. The supernatant fluid was injected in doses calculated according to the aforementioned formula.[2]

In order to compare the effects of spontaneous and those of induced hydronephrosis, experiments were also done on rats in which one ureter had been ligated two to seven days previously. The sensitivity of these animals to standard renal extract was compared with that of normal rats, and the pressor properties of saline extract of the normal and those of the saline extract of the obstructed kidney from the same rat were compared according to the indicated technic.

RESULTS

The Blood Pressure of Hydronephrotic Rats.—A comparison between 4 rats with well marked bilateral hydronephrosis, 5 rats with unilateral hydronephrosis and 1,207 rats without hydronephrosis is shown in chart 1. The values for the blood pressure of normal rats were obtained from animals used in acute experiments in this laboratory in which they were kept under environmental conditions similar to those of the hydronephrotic rats. The chart shows clearly that each of the 4 rats with bilateral hydronephrosis had well marked hypertension. Of the 5 rats with unilateral hydronephrosis, 2 had a blood pressure well within the normal range (115 and 125 mm. of mercury, respectively), and 3 had a blood pressure at the extreme upper limit of the normal range (155, 155 and 165 mm. of mercury, respectively).

Another difference sometimes noted between the normal and the hydronephrotic rats was the tendency for the latter to exhibit a steady spontaneous decline in blood pressure. Under the conditions of our experiments normal rats usually displayed relatively little decline in blood pressure during a period of an hour or more. Hydronephrotic rats, on the other hand, tended to have a maximal value for blood pressure immediately after insertion of the aortic cannula, after which a slow decline sometimes ensued. This difference is illustrated in chart 2.

The Sensitivity of Hydronephrotic Rats to Renal Pressor Substance.—Since it has been shown in a previous publication from this laboratory (Grossman and Williams [3]) that the age of the animal is an important

2. In order to allow for a greater amount of fibrous tissue in hydronephrotic than in normal kidneys, an attempt was made to estimate the amount of functioning renal tissue and to add to the abnormal kidneys sufficient saline solution so that the final ratio would be approximately 4 cc. of salt solution per gram of functioning renal tissue, this ratio being used also in the case of the normal kidneys. Such a procedure resulted in extracts which could not be regarded as strictly comparable in a quantitative sense. This objection, however, did not apply to the experiments done later on rats with one ureter ligated, for here the abnormal kidney weighed approximately the same as the opposite normal organ of the same animal and contained no excess of fibrous tissue.

3. Grossman, E. B., and Williams, J. R., Jr.: Relation of Age to Renal Pressor Substance, Arch. Int. Med., to be published.

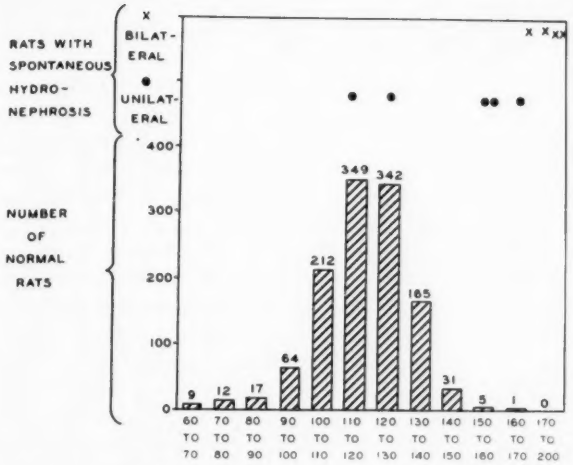

Chart 1.—A comparison of the blood pressures of 9 rats with spontaneous hydronephrosis with those of 1,207 normal rats. The figure illustrates the occurrence of hypertension in each of 4 rats with bilateral hydronephrosis and in 3 of 5 rats with unilateral hydronephrosis.

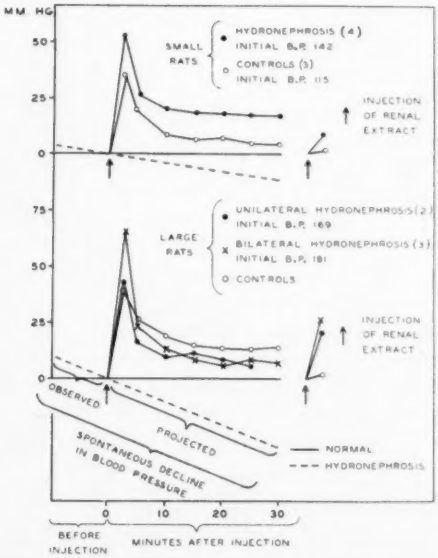

Chart 2.—Sensitivity of normal and of hydronephrotic rats to renal pressor substance. The injection of standard renal extract caused a greater initial rise in blood pressure in hydronephrotic than in normal rats. When allowance is made for the tendency of the blood pressure to decline spontaneously, the hydronephrotic animals also seemed to show a more sustained rise in blood pressure. A second injection of renal extract likewise produced a greater response than that which occurred in the control animals. The column of figures to the left shows the rise in mean arterial blood pressure after injection of renal extract.

factor in its sensitivity to renin, it was necessary, for purposes of comparison, to make observations on normal rats of approximately the same size and age as the hydronephrotic animals. Such comparisons are shown in chart 2. It can be seen that the initial rise in blood pressure was greater in the hydronephrotic than that in the normal rats. In the case of the small rats, with only slight elevation of blood pressure, the rise tended to be sustained for a longer time than it was in the controls. However, in the case of the larger rats, with more marked elevation of blood pressure, the rate of decline after the initial injection was more rapid in the controls. This rapid decline may have been an artefact, however, for, as has been pointed out, the hydronephrotic rats with well marked hypertension tended to show a spontaneous decrease in blood pressure. At the time of the injection of renal pressor substance their blood pressure was not constant but was slowly declining. Projection of the curves of their apparent rates of decline (the dotted lines in chart 2) suggests that actually these animals tended to display not only a greater initial rise in blood pressure but also a more sustained rise than did the normal controls. Furthermore, a second injection of renal pressor substance produced a distinctly greater rise in blood pressure in the hydronephrotic animals. The experiments indicate, we believe, that hydronephrotic rats are more sensitive than normal animals to renal extract.

The Pressor Effect of Saline Extracts of Hydronephrotic and of Normal Kidneys.—Chart 3 *A* shows a comparison of the responses produced in 3 normal rats by the injection of the extract of kidneys from animals with bilateral hydronephrosis with the effects produced in 3 other normal rats by the injection of extract of the kidneys from normal rats. The extract of the hydronephrotic kidneys caused a somewhat greater initial rise and a markedly greater sustained rise. Chart 3 *B* to *D* shows three comparisons of the saline extract of normal and that of hydronephrotic kidneys from the same rats. In each instance the extract of the diseased kidneys caused a greater rise in blood pressure. The experiments indicate clearly, we believe, that extract of hydronephrotic kidneys of hypertensive rats causes a greater pressor effect when injected into normal rats than does extract of normal kidneys.

Observations Made After Ureteral Ligation.—In order to determine whether the changes noted in animals with spontaneous hydronephrosis would occur when hydronephrosis was artificially produced, observations were made after ureteral ligation. It was found that slight but definite hydronephrosis developed within forty-eight hours. In the first experiment both ureters were ligated in 2 rats. Two days later the aorta was cannulated. One of the animals died during the operation. The remaining animal was compared with 3 normal rats as

regards sensitivity to renin. This animal displayed a somewhat greater initial response and a markedly greater sustained response than did any of the controls (chart 4).

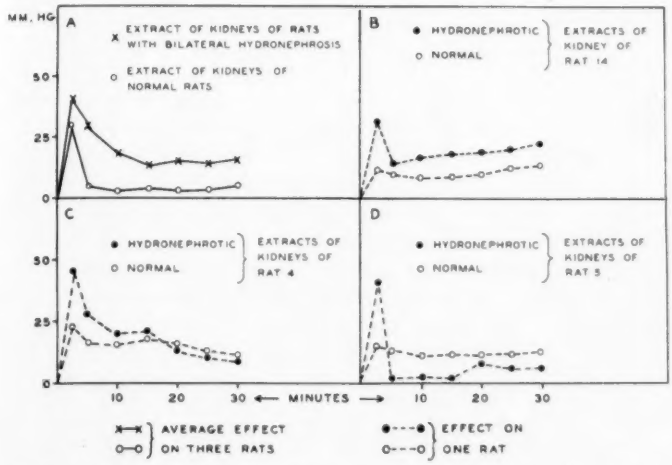

Chart 3.—Effect of saline extracts of normal and of hydronephrotic kidneys on the blood pressure of normal rats. Extract of hydronephrotic kidneys had a greater pressor effect than did extract of normal kidneys. The column of figures to the left shows the rise in mean arterial blood pressure.

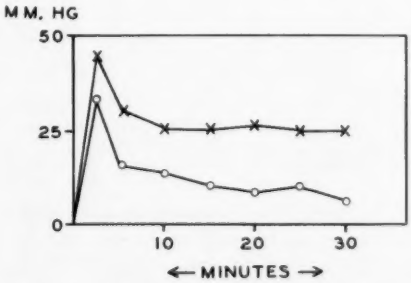

Chart 4.—Sensitivity of rats to renal pressor substances. The rat with both ureters ligated (the line with crosses indicates the values) displayed a greater response to standard renal extract than did the controls (the line with circles indicates the average values for 3 normal rats). The figures to the left show the rise in mean arterial blood pressure after injection of renal extract.

In order to avoid the complicating factor of uremia, observations were made after ligation of one ureter, the sensitivity of the animals

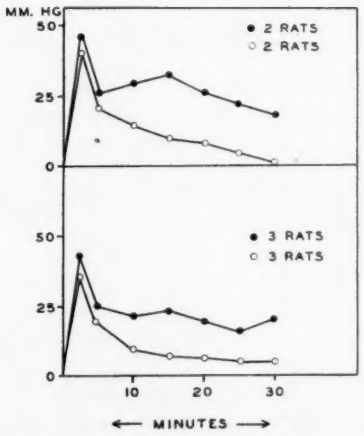

Chart 5.—Comparison of the sensitivity of normal rats (white circles) and that of rats with one ureter ligated (black circles) to renal pressor substance. Unilateral ureteral ligation caused increased sensitivity to renal pressor substance. The column of figures to the left shows the rise in mean arterial blood pressure after injection of renal extract.

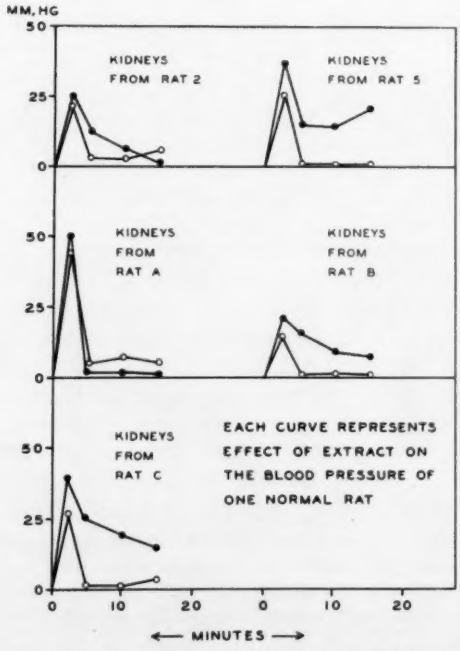

Chart 6.—Effects of saline extract of the normal (white circles) and that of the kidney with a ligated ureter (black circles) from the same rat on the blood pressure of normal rats. The extract of the abnormal kidney tended to have a greater pressor effect than did the extract of the opposite normal kidney. The column of figures to the left shows the rise in mean arterial blood pressure.

being determined two days later for one series of rats and four days later for another series. Both series of animals showed a slightly greater initial response to renin and a much more sustained rise in blood pressure than did the controls (chart 5). The average blood pressure of 2 rats after ligation of both ureters was 138 mm. of mercury. The average of 5 rats each with one ureter ligated was 122 mm., and that of 8 control animals was 127 mm.

Comparisons were made between the pressor effect of the saline extract of the normal and that of the obstructed kidney of the same rat in 5 instances. In each case the immediate pressor effect obtained from the kidney with a ligated ureter was somewhat greater than that produced by the extract of the normal kidney of the same animal. The abnormal kidney also produced a somewhat more prolonged pressor effect [4] (chart 6).

COMMENT

The data which have been reported indicate that rats with spontaneous hydronephrosis and rats with hydronephrosis induced by ureteral ligation are more sensitive than untreated rats of similar age and size to the injection of renal extract. They also show that extract of hydronephrotic kidneys, when injected into normal rats, tends to cause a greater pressor effect than does a similar extract of normal kidneys.

Our observations do not make it clear whether the most important factor is increased production in a hydronephrotic kidney of renal pressor substance or increased sensitivity of the rat to this substance. Perhaps both mechanisms are concerned. These cannot be the sole factors, however, for most of the rats with spontaneous hydronephrosis of only one kidney displayed hypertension, while animals with one ureter ligated, although showing increased sensitivity to renin and an increased amount of pressor substance in their kidneys, had no elevation of blood pressure. Apparently the duration of hydronephrosis is a factor of importance in determining whether or not hypertension occurs. Whether the hypertension displayed by the rats with spontaneous hydronephrosis was actually the result of increased formation of renal pressor substance or of heightened sensitivity to this substance is uncertain.

SUMMARY

Rats with spontaneous bilateral hydronephrosis display well marked elevation of blood pressure. Rats with spontaneous unilateral hydronephrosis may or may not have an elevated blood pressure. Hydro-

4. In several preliminary experiments it was found that the pressor effect of the fresh saline extract tended to change markedly after the material had stood in the room for several hours. Consequently, in these experiments the kidneys of a given rat were removed, ground and centrifuged, and the extract was injected immediately.

nephrotic rats respond to the injection of renal extract with a more marked rise in blood pressure than do normal rats of similar size and age. Extract of the abnormal kidneys of rats with spontaneous unilateral hydronephrosis produces greater pressor effects than does a similar extract of the normal kidneys of the same rats. Extract of the kidneys of rats with spontaneous bilateral hydronephrosis causes a greater rise in blood pressure than does extract of the kidneys of normal rats.

Ligation of one ureter for a period of several days causes slight hydronephrosis but no constant rise in blood pressure. After unilateral ureteral ligation the sensitivity of rats to renal pressor substance is somewhat greater than that of normal animals. Extract of the kidney rendered hydronephrotic by ligation of the ureter has a greater pressor effect than does a similar extract of the opposite normal kidney of the same animal.

FATAL ANAPHYLACTIC SHOCK IN MAN

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AND
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Complications arising from the injection of foreign proteins in man are relatively uncommon; sudden death following their administration may occur, but this is fortunately rare. Park [1] has estimated that fatal reactions due to serum therapy may take place once in 70,000 cases. The cases of fatal anaphylactic shock in man reported in the literature are few, and those in which an autopsy report is given are much less frequent. We feel, therefore, that the report of a fatal case with a pathologic study will be of interest, especially since our observations are similar to those described in cases of so-called thymic death.

REPORT OF A CASE

M. M., a Negress aged 39 years, was admitted to the hospital on May 27, 1937. About seven weeks before admission to the hospital she awoke one morning with stiffness of the joints. She was unable to raise her hands to her head and had considerable difficulty in walking. She stated that for the first four days of her illness she had some fever but since then had had a normal temperature. However, she still had some stiffness of the joints at the time of admission to the hospital. Her past history was essentially unimportant. No history of allergy was elicited.

Physical examination revealed a poorly developed and poorly nourished Negress who appeared chronically ill. The blood pressure was 132 systolic and 90 diastolic. The temperature and pulse rate were normal. The pupils were equal and reacted to light and in accommodation. The conjunctivas were pale. The nose, ears and mouth were normal. The neck and thorax showed no abnormality. The lungs were clear. The heart was within normal limits. The rhythm was regular, and a soft systolic murmur, which was not transmitted was heard at the apex. The abdomen revealed no abnormality. She had some difficulty in moving her joints. The reflexes were all present and normal but were somewhat diminished.

The urine was normal, and a Wassermann test of the blood gave a negative reaction. Roentgen examination of the joints showed atrophic changes.

It was decided to treat the patient's arthritis with foreign protein therapy. On May 29, 1 minim (0.06 cc.) of typhoid vaccine was given intravenously. She

From the Department of Pathology, Tulane University School of Medicine, and the Department of Pathology, State Charity Hospital of Louisiana.

1. Park, W. H.: Is Serum Anaphylaxis a Danger of Sufficient Importance to Limit Our Use of Protective Sera in the Treatment or Prevention of Diseases? Tr. A. Am. Physicians **28**:95, 1913; Antitoxin in Diphtheria, J. A. M. A. **76**:109 (Jan. 8) 1921.

reacted to this with a rise in temperature to 101.8 F.; by the next day the temperature was down to normal. On June 3, 2½ minims (0.15 cc.) of typhoid vaccine was given intravenously. After this treatment she told the intern that she had freer motion in the joints and that in general she felt much better. About thirty minutes after receiving the injection, while sitting on the edge of the bed, she suddenly complained of feeling ill and called for aid. By the time the nurse reached her side, the pulse was imperceptible, and death occurred shortly thereafter.

Autopsy.—The body was that of an underdeveloped and undernourished Negress about 40 years of age, weighing approximately 110 pounds (50 Kg.) and measuring 165 cm. in length. Moderate postmortem rigidity was present. The skin was dark brown and hung rather loosely owing to the loss of subcutaneous tissue. The joints showed no external abnormality. No other changes were noted on external inspection.

The heart weighed 325 Gm. The epicardium was smooth and glistening, and occasional petechiae could be seen beneath it. The right auricle and ventricle were markedly distended with blood, and the myocardium of the right ventricle was somewhat flabby. The left auricle and ventricle contained a few postmortem clots, and their walls were somewhat decreased in consistency. The valves and the endocardium were normal. The coronary vessels were patent throughout. The aorta showed an occasional atheromatous plaque.

The thymus gland appeared small and atrophic.

The lungs were gray and voluminous. The right lung weighed 475 Gm. and the left lung 350 Gm. Throughout the pleural surfaces, petechiae could be seen. When the pleural cavities were opened there was no evidence of collapse of the lungs. The lungs were moderately emphysematous, especially around their borders. The posterior portions of the lower lobes of both lungs were somewhat increased in consistency, and their cut surfaces showed some congestion. The rest of the lung tissue was well aerated. The mediastinal lymph nodes were enlarged and soft and showed some deposit of coal pigment.

The mesenteric vessels were congested. The spleen weighed 125 Gm. The capsule was blue, and the consistency of the organ was decreased. On section the parenchyma was pinkish red, and the malpighian corpuscles were prominent. The liver weighed 1,425 Gm., and the capsule was smooth and transparent. The consistency of the organ was decreased, and the cut surface showed marked congestion. The right kidney weighed 145 Gm. and the left kidney 155 Gm. The capsules were thin and stripped with ease, leaving a smooth cortical surface. The cut surfaces showed no distortion of the architecture, but considerable congestion was present. The gastrointestinal tract was markedly congested. The lymphoid follicles throughout the tract, but especially in the rectum, were prominent. The lymph nodes in the mesentery of the small intestine and along the abdominal aorta were enlarged, gray and soft.

The pancreas, adrenal glands, gallbladder, urinary bladder and genital organs were grossly normal.

The vessels of the dura, sinuses and surfaces of the brain were markedly congested. The leptomeninges were smooth and glistening. The gyri were not flattened, and the sulci were wide and deep. The cut surfaces of the brain showed some congestion.

Microscopic Observations: In different microscopic fields of the sections of the lungs varying changes could be seen. In many instances the alveoli were of normal size, while the alveolar capillaries showed a moderate degree of dilatation. In other portions of the sections these capillaries were engorged with blood, and the alveoli were flattened (fig. 1 *A*). No areas of complete collapse of the

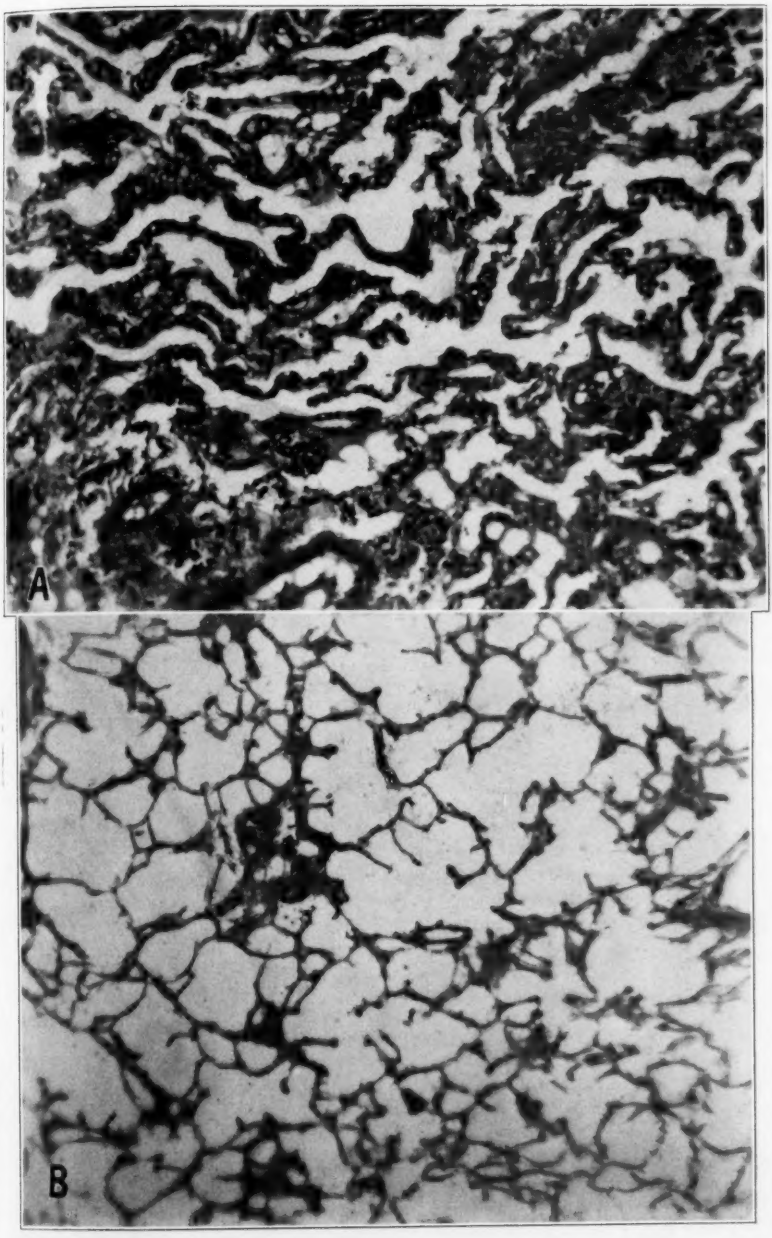

Fig. 1.—*A*, section of the lung showing compressed alveoli with congested capillaries. *B*, section of the lung showing dilated alveoli and ruptured alveolar walls.

alveoli were noted. Areas were also seen where the alveoli were dilated, and in some instances their walls were ruptured (fig. 1 *B*). Here and there, areas were seen where the alveoli were filled with serum, some red blood cells and an occasional leukocyte. Other alveoli were noted which contained some large mononuclear cells and a few leukocytes. Throughout the lungs the capillaries were dilated, but this was least so in the walls of the distended alveoli. Many of the capillaries contained a moderate number of leukocytes, and among these an occasional eosinophil could be seen. Some arterial walls were slightly thickened, and a few arteries were noted which were filled with many leukocytes, mainly neutrophils, with an occasional eosinophil (fig. 2). The epithelium lining a few

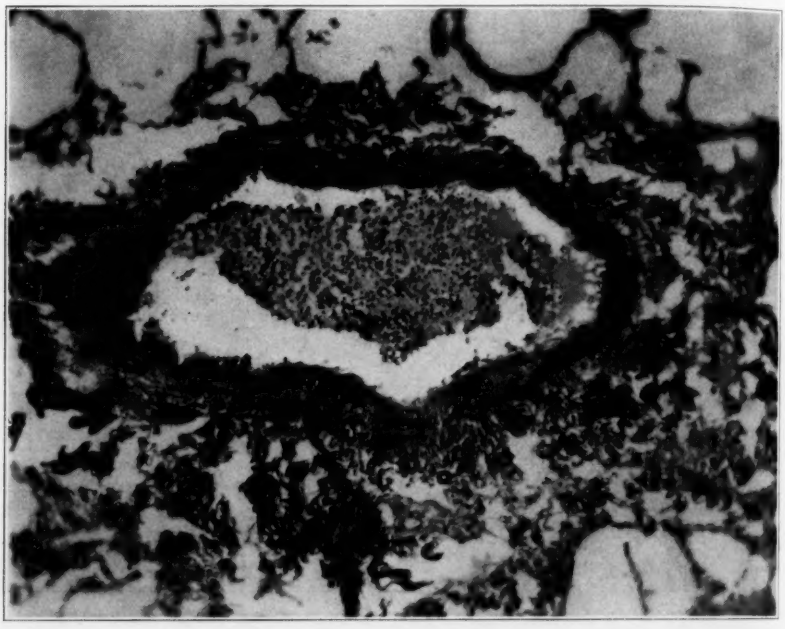

Fig. 2.—A pulmonary artery filled with many neutrophils and an occasional eosinophil.

bronchioles was arranged in fairly deep folds, and the lumen was slightly narrowed. Numerous small lymphocytic accumulations were seen in the peribronchial tissues throughout the sections.

The sinusoids of the liver were considerably dilated. They were engorged with blood and contained a moderate number of leukocytes (fig. 3 *A*). The distribution of the leukocytes was uneven, in that they were found in greater numbers in the sinusoids about the portal canals. The central veins were dilated and congested with red blood cells and some leukocytes. Examination of the leukocytes within the sinusoids revealed a number of mononuclear leukocytes, a moderate number of neutrophils and an occasional eosinophil (fig. 3 *B*). The branches of

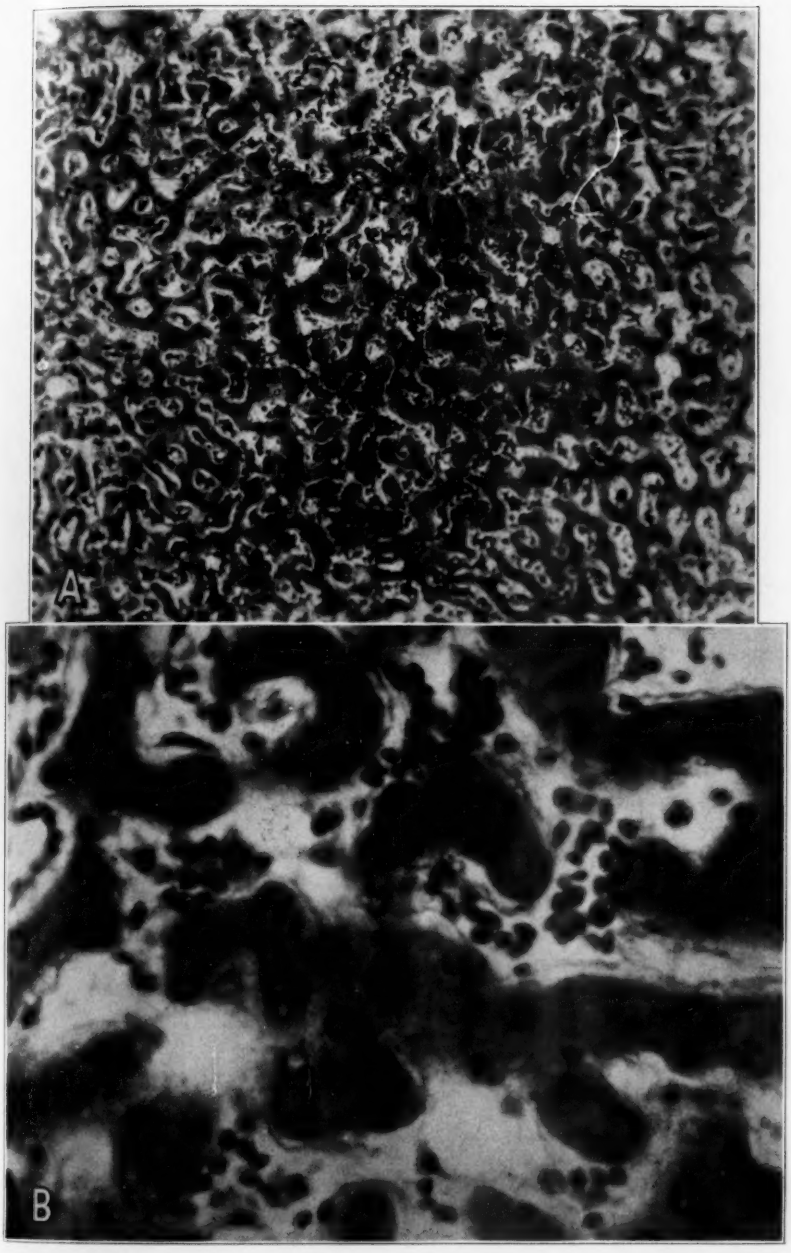

Fig. 3.—*A*, section of the liver showing engorged sinusoids. *B*, a view under higher power of hepatic sinusoids showing numerous leukocytes.

the portal vein were also congested with red blood cells and an occasional leukocyte. The Kupffer cells appeared somewhat enlarged and were separated from the adjacent hepatic cells. The hepatic cells were enlarged, and their cytoplasm was granular and in some areas vacuolated. Some of the nuclei were large and clear, while others were homogeneously dark. A considerable amount of yellow pigment was seen within the hepatic cells, especially the Kupffer cells.

The splenic pulp showed moderate congestion with red blood cells. The malpighian corpuscles were markedly enlarged and had large germinal centers (fig. 4). There was no excess of neutrophils within the splenic pulp.

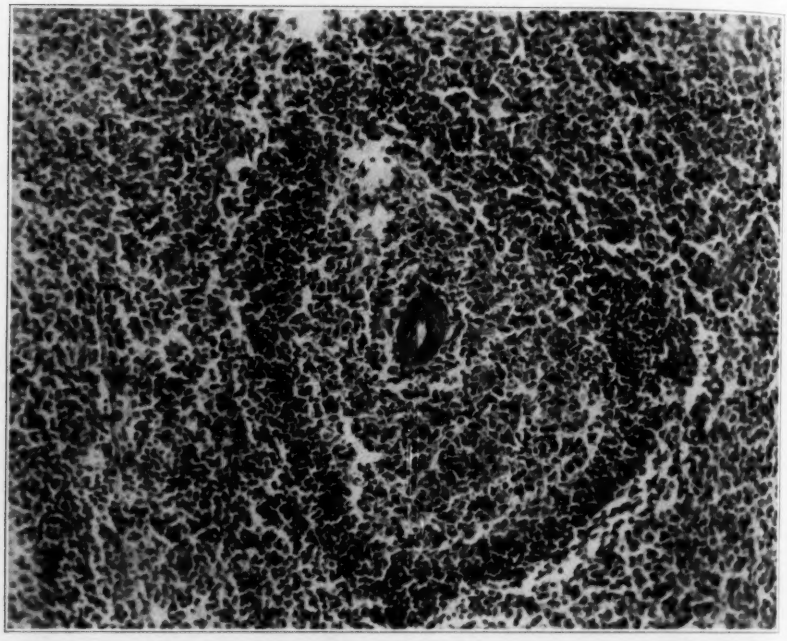

Fig. 4.—A splenic corpuscle with a large germinal center.

The myofibrils of the heart revealed no abnormal changes. The cross striations were well preserved. The blood vessels were slightly dilated and congested with red blood cells and an occasional leukocyte.

In the kidneys an occasional hyalinized glomerular tuft was noted. The capillaries, arteries and veins were all dilated and congested with red blood cells. The tubular cells showed no pathologic changes.

The glandular epithelium of the rectum was normal. All the blood vessels were dilated and congested with red blood cells and an occasional leukocyte. The lymphoid follicles were markedly enlarged.

Sections from the brain, adrenal glands, pancreas, thymus and lymph nodes showed marked congestion of the blood vessels.

COMMENT

The anatomic changes observed in our case agree in many respects with those observed in some animals [2] and in human beings [3] after anaphylactic death. However, postmortem observations reported in the literature on sudden death following injection of a foreign protein show no marked constancy. Such changes as emphysema with bronchiolar contraction and thickening of the arterioles of the lung, dilatation of the right side of the heart, congestion of the liver and other internal organs and enlargement of the thymus have been reported in various cases.

Much experimental work has been done on anaphylaxis in animals. The symptoms of acute anaphylactic shock vary markedly in the different species of animals and depend largely on a difference in the underlying pathologic changes occurring in the respective species. The difference depends on the location of the "shock organ" or "tissue." In the guinea pig the tissue acted on is the bronchial musculature, which contracts and causes death by asphyxia. The "shock tissue" in the rabbit is the muscle of the pulmonary artery, and death occurs as a result of the cessation of the pulmonary circulation because of mechanical interference. In the dog the liver is the important "shock organ," and death is brought about by the sudden accumulation of most of the animal's blood in the liver and abdominal veins as a result of obstruction to the circulation in the hepatic vein. This obstruction is due to contraction of the musculature of the vein or to swelling of the capillary endothelium, but which is the more important factor has not been definitely established. That the former is more important is the view held by most investigators. This phenomenon causes marked lowering of the systemic blood pressure, and this is further depressed by the action of hepatogenous substances on the systemic terminal vessels, causing their dilatation.

Much of the work on anaphylaxis in dogs has been done by Weil.[2] The changes that he observed were similar to those noted in the case herein reported. It seems likely that the cause of death in this case was due to a fall in blood pressure caused by dilatation of the sinusoids of the liver and of the abdominal veins and possibly of the capillaries of the lung. This drop in blood pressure caused anoxemia of the respiratory centers in the medulla, with cessation of respiratory movements, and cardiac failure. The collection of leukocytes in the liver and lung may be related to the leukopenia of the peripheral blood observed in cases of anaphylactic shock, and the eosinophils noted suggest an allergic background.

2. Weil, R.: Studies in Anaphylaxis: XXI. Anaphylaxis in Dogs; a Study of the Liver in Shock and in Peptone Poisoning, J. Immunol. **2**:525, 1917.

3. Dean, H. R.: The Histology of a Case of Anaphylactic Shock Occurring in a Man, J. Path. & Bact. **25**:305, 1922.

Cases have been reported of fatal anaphylactic shock in man in which the mechanism was that of the "guinea pig type," [4] namely, bronchiolospasm with respiratory failure. It may therefore be assumed that the mechanism in man may vary in different cases, being of one of at least two types, either the bronchiolospastic or the splanchnic type.

Waldbott [5] has made some interesting observations concerning the relation between anaphylaxis and status lymphaticus. He studied a number of cases in which the diagnosis of "thymic death" had been made and observed uniform changes in the lungs, namely, edematous, hemorrhagic areas in the alveoli, emphysema alternating with atelectasis and occasional eosinophilic cells. These changes were similar to those reported in the literature in many cases of fatal anaphylactic shock in man. He observed similar changes in the lungs of infants with true allergic asthma. Waldbott and Anthony [6] have noted, further, that in children with enlargement of the thymus, true allergic asthma develops later in life. Waldbott [7] has suggested that "thymic death" may be a preallergic phenomenon which is probably identical with anaphylactic shock; as the body has not yet set up a sufficient defensive mechanism against the invading antigen, the patient therefore dies suddenly instead of having an asthmatic attack.

SUMMARY

A case of fatal anaphylactic shock following the second intravenous injection of a foreign protein is reported, with necropsy observations.

The gross pathologic changes were marked congestion of the liver and more moderate congestion of the other organs. General enlargement of the lymph nodes and a persistent thymus gland were also noted.

The significant microscopic changes were dilatation and congestion of the hepatic sinusoids and the alveolar capillaries of the lungs. There was an apparent relative increase in the leukocytes and the eosinophils within these vessels. The alveoli were compressed in some areas and dilated in others, and in some instances their walls were ruptured. The malpighian corpuscles of the spleen were increased in size and had large germinal centers.

It is suggested that the mechanism of death in this case was of the so-called "dog" type, namely, capillary dilation, especially of the liver, with a corresponding fall in blood pressure and cardiac failure.

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4. Sheppe, W. M.: Fatal Anaphylaxis in Man, J. Lab. & Clin. Med. **16**:372, 1931.

5. Waldbott, G. L.: So-Called "Thymic Death": VI. The Pathologic Process in Thirty-Four Cases, Am. J. Dis. Child. **47**:41 (Jan.) 1934.

6. Waldbott, G. L., and Anthony, G. E.: So-Called Thymic Hyperplasia: IV. A Follow-Up Study of Thirty Cases, Am. J. Dis. Child. **47**:34 (Jan.) 1934.

7. Waldbott, G. L.: The Allergic Theory of So-Called Thymic Death, J. A. M. A. **105**:657 (Aug. 31) 1935.

CORONARY OCCLUSION WITH AND WITHOUT PAIN

ANALYSIS OF ONE HUNDRED CASES IN WHICH AUTOPSY WAS DONE WITH REFERENCE TO THE TENSION FACTOR IN CARDIAC PAIN

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In the early years of the clinical recognition of coronary occlusion, substernal or epigastric pain of at least several hours' duration was considered to be a characteristic feature. Subsequent observations have shown not only that this type of pain may be closely simulated by other conditions, such as acute surgical disorders of the abdomen, pulmonary embolism, dissecting aneurysm of the aorta, interstitial emphysema and pneumothorax, but also that painless occlusion of the coronary artery may occur in a certain number of cases, with dyspnea replacing pain most frequently as the presenting symptom. The clinical picture here is that of failure of the left ventricle, followed by congestive heart failure. In a still smaller percentage of cases the severe initial anginal pain may be replaced by symptoms suggesting a cerebral vascular lesion, such as sudden weakness, dizziness, syncope and unconsciousness, or by gastrointestinal features, such as nausea, vomiting, distention, obstipation and abdominal pain. The rather high incidence of cardiac infarction without pain is not, however, generally recognized. Recently the number of published reports dealing with this fact has been increasing. White,[1] for example, has emphasized the importance of the nonpainful features of coronary occlusion, and the rather frequent occurrence of cardiac infarcts without pain is evidenced by numerous case reports.[2] To our knowledge, few reports of large series

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Presented in abstract form at the Fifty-Third Annual Meeting of the Association of American Physicians, Atlantic City, N. J., May 3, 1938.

1. White, S. M.: Non-Painful Features of Coronary Occlusion, Ann. Int. Med. **8**:690-700, 1934.

2. (*a*) Barnes, A. R.: Acute Coronary Occlusion Without the Characteristic History of Anginal Pain: Course, Treatment and Electrocardiographic Findings, M. Clin. North America **18**:477-489, 1934. (*b*) Bramwell, C.: British Medical Association Lecture on Coronary Occlusion, Brit. M. J. **1**:681-685, 1930. (*c*) East, C. F. T.; Bain, C. W. C., and Cary, F. L.:: Cardiac Infarction Without Pain,

(Footnote continued on next page)

of cases with autopsy data have thus far been published in which this particular point is considered. Wearn,[3] for instance, reported that in 53 per cent of 19 cases, the diagnosis being confirmed by necropsy, there was absence of pain. In a series of 76 cases, with autopsy performed in 53 cases, Davis [4] found pain present in 21 cases (40 per cent) and absent in 21 cases (40 per cent), sudden death preventing the recording of an adequate history regarding pain in 11 others. If these cases are excluded, painless occlusion occurred in 50 per cent of this series. Recently Bruenn, Turner and Levy [5] concluded from a clinicopathologic study of 476 cases of disease of the coronary arteries that the incidence of cardiac pain varies, depending on the type and the location of the fundamental lesion. Thus 12 (39 per cent) of a group of 31 patients with proved thrombosis had pain, and 19 (61 per cent) did not. Katz and his associates [6] reported that there was no history of pain in 13 of a group of 34 cases in which the heart was examined post mortem, an incidence of 38 per cent. Kennedy,[7] in a recent communication, suggested that the occurrence of coronary thrombosis without any painful or uncomfortable sensations is by no means as common as has been described in the foregoing reports. In a series of 200 cases in which there were 109 old and 142 recent infarcts, he found, after excluding 48 cases because of unsatisfactory histories, that "Ninety-one per cent of the recent and 64 per cent of the old infarcts had the classical pain of a coronary attack."

Lancet **2**:60-63, 1928. (*d*) Herrmann, G. R.: Synopsis of Diseases of the Heart and Arteries, St. Louis, C. V. Mosby Company, 1936, p. 214. (*e*) Parkinson, J., and Bedford, D. E.: Cardiac Infarction and Coronary Thrombosis, Lancet **1**:4-11, 1928. (*f*) Smith, H. L., and Brink, J. R.: Acute Coronary Thrombosis Without Characteristic Pain and Without Symptoms of Shock, Minnesota Med. **19**:346-349, 1936. (*g*) Stenn, F.: Painless Coronary Occlusion, Illinois M. J. **67**:381-382, 1935. (*h*) Menard, O. J., and Hurxthal, L. M.: Painless Coronary Thrombosis as a Post-Operative Complication, S. Clin. North America **11**:395-401, 1931. (*i*) Boyd, L. J., and Warblow, C. W.: Coronary Thrombosis Without Pain, Am. J. M. Sc. **194**:814-824, 1937.

3. Wearn, J. T.: Thrombosis of the Coronary Arteries with Infarction of the Heart, Am. J. M. Sc. **165**:250-276, 1923.

4. Davis, N. S., III: Coronary Thrombosis Without Pain: Its Incidence and Pathology, J. A. M. A. **98**:1806 (May 21) 1932.

5. Bruenn, H. G.; Turner, K. B., and Levy, R. L.: Notes on Cardiac Pain and Coronary Disease: Correlation of Observations Made During Life with Structural Changes Found at Autopsy in Four Hundred and Seventy-Six Cases, Am. Heart J. **11**:34-40, 1936.

6. Saphir, O.; Priest, W. S.; Hamburger, W. W., and Katz, L. N.: Coronary Arteriosclerosis, Coronary Thrombosis, and the Resulting Myocardial Changes, Am. Heart J. **10**:567-595 and 762-792, 1935.

7. Kennedy, J. A.: The Incidence of Myocardial Infarction Without Pain in Two Hundred Autopsied Cases, Am. Heart J. **14**:703-709, 1937.

Our own clinical impression that painless closure of the coronary artery was not infrequent has been confirmed by an analysis of a series of 100 cases in which autopsy was performed. The generally accepted theories of cardiac pain do not offer a completely satisfactory explanation, in our opinion, for the presence of pain in some instances of cardiac infarction and its absence in others. The present study was undertaken, therefore, in order to correlate the clinical and the pathologic data in a large series of proved cases, with the hope that some light might be shed on the factors concerned in this problem.

CLINICOPATHOLOGIC STUDY

The patients included in this analysis were drawn from the medical service of the Albany Hospital and from the private services of a number of our associates.[8] The complete pathologic reports, made by members of the department of pathology of the Albany Medical College, were placed at our disposal by Prof. A. W. Wright. During the years 1917 to 1937, 3,040 postmortem examinations were performed in this department, and the diagnosis of coronary thrombosis or cardiac infarction was made in 140 instances (4.6 per cent). We have used the term coronary occlusion because it is more comprehensive. It includes obstruction of the coronary artery due to thrombosis, fibrotic narrowing and embolism. The result of such obstruction is a cardiac infarct, provided sufficient time elapses before death for its development. The case histories of these 140 patients were carefully reviewed, together with the autopsy protocols, and the primary cause of death was established in each case. This procedure resulted in the elimination of 40 cases for the following reasons: (1) 8 examples of the focal or embolic type of scarring in the myocardium with infarcts less than 1 cm. in diameter; (2) 25 instances of old or recent cardiac infarction in which death was due clearly to some other pathologic condition, such as pneumonia, peritonitis, postoperative shock, fracture of the skull, cerebral hemorrhage, multiple pulmonary infarcts, advanced pulmonary tuberculosis, carcinoma of the prostate, diabetic coma, uremia, septicemia or pneumococcic meningitis, and (3) 7 instances of sudden death due to cardiac infarction in which records of the history, physical examination or medical observation before death were lacking. This left a group of 100 patients, coronary occlusion being the primary cause of death in 80 instances, a definitely contributory cause in 15 and a probable cause in 5. Gross infarcts, measuring more than 1 cm. in diameter, with palpable areas of softening or fibrosis in the myocardium, were present

8. The following physicians gave us permission to include their cases in this study: Drs. G. E. Beilby, K. E. Crounse, J. L. Donhauser, A. W. Elting, F. N. Guyer, J. L. Hemstead, H. H. Hun, F. B. Maguire, C. E. Martin, Thomas Ordway, A. H. Traver, J. A. Sampson, A. H. Stein, C. K. Winne Jr. and L. H. Ziegler.

in all except 2 cases, in which the thrombosis of the coronary artery had apparently been too recent for infarction to occur. Pulmonary infarcts secondary to cardiac infarction were found in 15 instances. There was only 1 case of true syphilitic aortitis in the series with actual destruction of the media of the arterial wall. There were 2 examples of old rheumatic heart disease, with superimposed arteriosclerotic heart disease. There was 1 instance of periarteritis nodosa. Arteriosclerotic changes in the coronary arteries of the same general nature were present in the entire series, with the exception of the aforementioned case of periarteritis nodosa. It was not possible to separate sharply the cases of hypertensive cardiovascular disease with marked

TABLE 1.—*Analysis of Clinical Findings for One Hundred Patients with Coronary Occlusion with Cardiac Infarction*

Division of Patients	Age		Sex		History of Preceding Attacks of Cardiac Pain		Dyspnea as an Outstanding Symptom		History of Hypertension		Pericardial Friction Rub	
	Decades	No. of Patients	Males	Females	Positive	Negative	Present	Absent	Positive	Negative	Present	Absent
Group 1:	31-40	2	1	1								
58 patients	41-50	4	3	1	35	23						
with cardiac	51-60	25	21	4	..	..	9	49				
infarction	61-70	18	12	6	..	..	..	..	21	37		
with pain	71-80	9	5	4	..	..	..	..	..	..	7	51
	81-90	0	0	0								
Percentage					60	40	15	85	36	64	12	88
Group 2:	31-40	1*	1*	0	8	34						
42 patients	41-50	3	3	0	..	..	26	16				
with cardiac	51-60	9	8	1	..	..	..	..	7	35		
infarction	61-70	14	7	7								
without pain	71-80	12	7	5	..	..	..	..	..	..	1	41
	81-90	3	2	1								
Percentage		100	70	30	19	81	62	38	17	83	2	98

* One patient had periarteritis nodosa.

coronary sclerosis from those of pure arteriosclerotic heart disease with changes in the coronary arteries but no hypertension. Most of the patients were admitted to the hospital with a falling or low blood pressure.

For the purpose of analysis these 100 patients were divided into two groups: (1) those who had cardiac pain in the final attack and (2) those who did not. Certain pertinent clinical facts were then correlated with the postmortem reports, and the results are summarized in tables 1 and 2. In the first group were included all patients who complained of pain even of minimal degree in the substernal, precordial or epigastric region, as well as in the shoulders, arms, wrists, jaws or scapulas. Vague discomfort or a sense of pressure or constriction in the chest was not recorded as pain. No systematic study was made of the relative sensitivity to painful stimuli of the patients in these

TABLE 2.—*Analaysis of Postmortem Data for One Hundred Patients with Coronary Occlusion with Cardiac Infarction*

Division of Patients	Description of Infarct				Location of Infarct						Acute Pericarditis		Cardiac Rupture with Hemoperi-cardium		Thrombosis of Coronary Artery		Degree of Coronary Sclerosis	
	Acute	Old	Acute and Old	Absent	Anterior Apical	Midventricular	Posterior Basal	Anterior Apical, and Midventricular	Anterior Apical, Midventricular and Posterior Basal	Anterior Apical, and Posterior Basal	Present	Absent	Present	Absent	Present	Absent	Mild to Moderate	Marked
Group 1: 58 patients with cardiac infarction with pain	20	11	26	1	39	2	4	3	2	7	25	29	6	52	33	25	13	45
Percentage	35	19	46	..	67	..	..	..	..	..	43	50*	..	..	57	43	22	78
Group 2: 42 patients with cardiac infarction without pain	5	18	18	1	26	3	7	0	0	5	8	29	3	39	13	29	5	37†
Percentage	12	44	44	..	62	..	..	..	..	..	19	69‡	..	..	31	69	12	88

* Four patients (7 per cent) had chronic adhesive pericarditis.
† One patient had periarteritis nodosa.
‡ Five patients (12 per cent) had chronic adhesive pericarditis.

two groups. Although such differences, as pointed out by Libman,[9] undoubtedly exist, it is to be noted that several of the patients who died in a painless attack of coronary occlusion had been previously seen by us when they complained of severe pain because of other conditions, such as herpes zoster, tabes dorsalis and carbuncle. Furthermore, it seems probable that although the severity of cardiac pain may be definitely less in some hyposensitive patients, it would not be safe to assume that this reduced sensitivity could alone explain the complete absence of cardiac pain in certain fatal attacks of coronary occlusion. In addition to this, 19 per cent of the patients included in the second group, as will be described later, gave a history of definite anginal pain previous to the final fatal attack.

INCIDENCE, AGE AND SEX

In our series of 100 patients with coronary occlusion, 42 suffered fatal attacks which were unaccompanied by pain, while the remaining 58 complained of cardiac pain of varying location, intensity and duration. It is to be noted that 30 of the 40 patients excluded for the reasons previously indicated did not have pain. Had these been included in the series the percentage of cases of painless infarcts would have been considerably greater. In 66 per cent of the cases death occurred between the fiftieth and the seventieth year. Males apparently tended to die about a decade earlier than females, the peak mortality for the former being reached at approximately 55 years and for the latter at 65 years (chart 1). Of the 58 patients who died in a painful attack of coronary occlusion, 43 (74 per cent) succumbed between the ages of 50 and 70; while of the 42 patients who died without pain, 23 (55 per cent) succumbed in the sixth and seventh decades. For the more advanced decades, aged 70 to 90, painful occlusion occurred in 9 of 58 patients (16 per cent) and painless occlusion in 15 of 42 patients (36 per cent). Thus it appears that painful attacks tend to occur somewhat more frequently in the earlier decades (51 to 70 years) and that painless seizures show a higher incidence in the advanced decades (71 to 90 years; chart 2). Males experienced their fatal and painful coronary occlusion ten years earlier than did females (chart 3). The same relation between the sexes existed in the group with painless attacks (chart 4).

HISTORY OF PRECEDING ATTACKS

In studying the past histories of the 58 patients in group 1, who died in a painful attack, it was interesting to find that 35 (60 per cent) had been the subject of one or two previous painful seizures and 23

9. Libman, E.: Observations on Individual Sensitiveness to Pain, J. A. M. A. **102**:335-341 (Feb. 3) 1934.

(40 per cent) had never before suffered from severe stenocardia.[10] Of the 42 patients comprising group 2, who died in a painless attack, there was a history of preceding anginal pain for only 8 (19 per cent), with no record of its occurrence in 34 (81 per cent). It seems that if

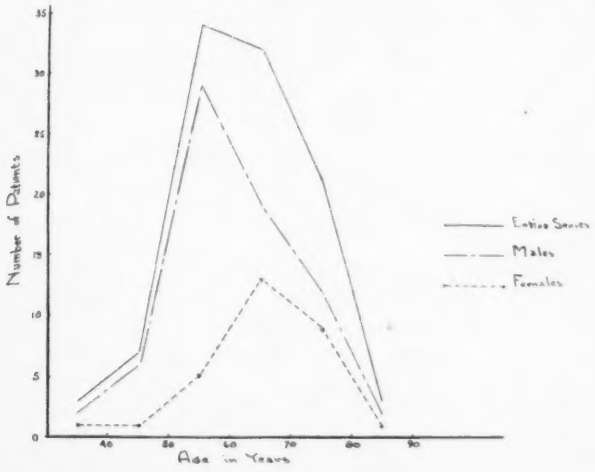

Chart 1.—Age-sex correlation in 100 cases of coronary occlusion.

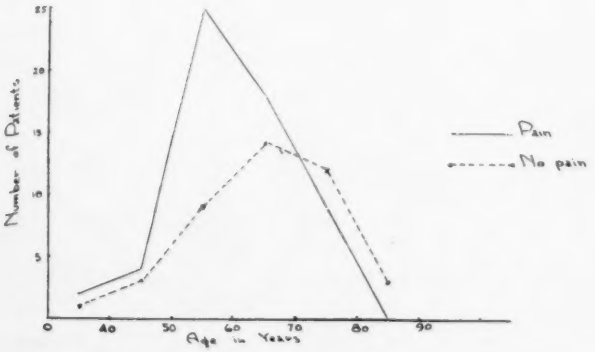

Chart 2.—Age-sex correlation of painful and painless coronary occlusion.

a patient with progressive disease of the coronary arteries has one or more attacks of severe substernal pain and recovers, he is more likely

10. It was not possible to conclude whether the pain was that of coronary occlusion or of angina pectoris in many cases.

than not to suffer pain in his last or fatal attack. On the other hand, if advancing disease of the coronary arteries manifests itself only by dyspnea and diminishing cardiac function, the patient so afflicted is more prone to die with a painless cardiac infarct. This deduction is similar to that of Bruenn and his associates,[5] who reported that in their experience the patients who had no symptoms prior to the acute episode were most likely not to have pain associated with it.

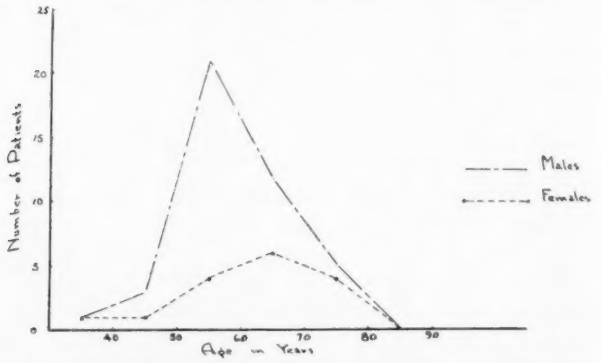

Chart 3.—Age-sex distribution in 58 cases of painful coronary occlusion.

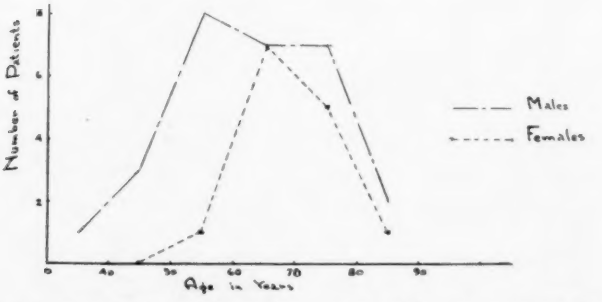

Chart 4.—Age-sex distribution in 42 cases of painless coronary occlusion.

DYSPNEA

Dyspnea was the outstanding symptom of only 9 (15 per cent) of the 58 patients in group 1 (patients with painful occlusion). In contrast with this, dyspnea, although often present in the remaining 49 patients (85 per cent) of this group, was overshadowed by pain. In group 2, comprising 42 patients with painless occlusion, there were 26 instances (62 per cent) in which dyspnea was the dominant symp-

tom. In 16 cases (38 per cent) dyspnea when present was of minor degree. From this evidence one may see that when pain occurs in cardiac infarction this symptom overshadows dyspnea in more than four fifths of the cases. Conversely, it is clear that in coronary closure unaccompanied by pain, dyspnea becomes a rather prominent and outstanding symptom in approximately two thirds of the cases. This observation is in accord with that originally made by Obrastzow and Straschesko,[11] who stated that dyspnea may be the pain equivalent.

HYPERTENSION

In group 1 there were 21 patients (36 per cent) with a history of preceding hypertension, while in group 2 there were only 7 (17 per cent). Of a total of 28 patients in the two groups with a history of preceding hypertension, 21 (75 per cent) had pain accompanying coronary occlusion. It appears that previous hypertension is about three times more frequent in the group of patients who had painful attacks.

PERICARDIAL FRICTION RUB

A pericardial friction rub was heard in 7 patients (12 per cent) belonging to group 1 and in 1 patient (2 per cent) in group 2. Of a total of 8 instances in which audible friction was recorded, 7 (88 per cent) occurred in patients with painful occlusion (group 1). Although the evanescent nature of this clinical sign is fully appreciated, it appears to be decidedly more common in patients experiencing painful cardiac infarction.

TYPE OF INFARCTION

The 98 patients[12] were divided into three classes, viz., class A, those showing recent or acute infarcts; class B, those presenting old or healed infarcts, and class C, those having both acute and old infarction. In group 1, comprising 57 patients with painful coronary occlusion, there were 20 with acute infarcts (35 per cent), 11 with old infarcts (19 per cent) and 26 (46 per cent) with combined acute and old infarcts. Combining classes A and B, one finds that acute infarction was present actually in 46 of the 57 patients (81 per cent) in group 1 and old infarction in only 11 patients (19 per cent).

In group 2, including 41 patients with painless coronary occlusion, there were 5 (12 per cent) with acute, 18 (44 per cent) with old healed infarcts and 18 (44 per cent) with the combined type of infarct (acute and old). Combining classes A and C, it is seen that 23 patients

11. Obrastzow, W. P., and Straschesko, N. D.: Zur Kenntnis der Thrombose der Koronarterien des Herzens, Ztschr. f. klin. Med. **71**:115-132, 1910.

12. Two patients did not have a gross infarct, death occurring before it developed.

(56 per cent), or slightly over half of those in group 2, had acute infarction but in spite of this did not experience pain.

Viewed in another way, of the total of 69 patients with actual acute infarction in the entire series, two-thirds were in group 1 and one-third in group 2. Of 29 patients with old infarcts, however, approximately two-thirds fell in group 2 and one-third in group 1. Thus it appears that while acute infarcts tend to be accompanied by pain and old ones do not, there must still be some other factor conditioning the production of pain in coronary occlusion. Kennedy,[7] as previously stated, found in a series of 200 cases that pain was more frequently present with recent than with old infarcts.

LOCATION OF INFARCT

Cardiac infarcts were present most frequently in the anterior apical region. The incidence of infarction located in this area in the patients with painful attacks and in those without them was almost identical: group 1, 39 patients (67 per cent); group 2, 26 patients (62 per cent). The location of the infarct in this region therefore appears to bear no relation to the presence or absence of pain. With regard to the other sites of infarction, i. e., the midventricular and posterior basal regions of the heart, there were too few cases for analysis. Likewise, no conclusions could be drawn from the 17 cases in which infarcts were present in two or three sites. Bruenn and his associates [5] found no causal relation between pain and the particular artery or branch occluded.

Opinion is apparently divided on the question of the relative frequency of the occurrence of infarcts in the anterior apical midventricular and posterior basal regions of the heart. One group of authors [13] have reported that in the large majority of their cases the apical portion of the left ventricle was involved, while another group [14] have reported that the midventricular and posterior basal regions taken together were the site of the lesion in over half the cases.

ACUTE PERICARDITIS

In group 1 there were 22 patients (38 per cent) with acute pericarditis, 4 with chronic pericarditis, 3 with both acute and chronic pericarditis and 29 with no pericarditis. In group 2 there were 5

13. Levine, S. A.: Coronary Thrombosis: Its Various Clinical Features, Medicine Monograph, Baltimore, Williams & Wilkins Company, 1929, vol. 16. Gorham, L. W.; Ordway, T.; Jacobsen, V. C., and Hosoi, K.: The Pathology of Cardiac Infarction, Tr. Am. Climat. & Clin. A. **48**:105-113, 1932.

14. Barnes, A. R., and Ball, R. G.: Incidence and Situation of Myocardial Infarction in One Thousand Consecutive Post-Mortem Examinations, Am. J. M. Sc. **183**:215-225, 1932. Parkinson and Bedford.[2e]

patients with acute pericarditis, 5 with chronic pericarditis, 3 with acute and chronic pericarditis and 29 with no evidence of pericarditis. Acute pericarditis was present in 43 per cent of the patients in group 1 and in only 19 per cent of those in group 2. Of a total of 33 instances of acute pericarditis, 25 (75 per cent) occurred in patients in group 1. It is evident that acute pericarditis is commonly present in painful coronary occlusion and often absent in the painless attacks, but it is equally apparent that this fact alone does not explain the presence or absence of pain.

CARDIAC RUPTURE WITH HEMOPERICARDIUM

Cardiac rupture with hemopericardium occurred in 9 patients in the series of 100, 6 belonging in group 1 and 3 in group 2. The total number of patients is too small to permit one to draw definite conclusions. Cardiac rupture, however, does not seem to have any significant bearing on the presence of pain in coronary occlusion.

THROMBOSIS OF THE CORONARY ARTERY

In group 1, 33 of the 58 patients with painful attacks (approximately 57 per cent) showed at autopsy thrombosis of a coronary artery. Among 42 patients in group 2, who were without pain, thrombosis occurred in 13 instances (31 per cent). If the total number of patients in groups 1 and 2 who showed actual thrombosis are considered, it is found that in 33 of the 46 patients (72 per cent) the thrombosis was characterized by pain and that in 13 (28 per cent) it was not. This suggests that thrombosis per se when present in a coronary artery carries with it a two and a half to one chance of causing a painful seizure. The reverse of this, however, is not true, i. e., that absence of actual thrombosis means probable absence of pain. Of 54 patients in the two groups with no evidence of thrombosis, pain was present in 25 (46 per cent) and absent in 29 (54 per cent). Although actual acute thrombosis favors the occurrence of pain, absence of it by no means excludes the possibility of pain. It is reasonable therefore to suppose that there is still another factor besides thrombosis on which the initiation of cardiac pain depends. Bruenn, Turner and Levy[5] stated: "It was only when the vessel was actually occluded, either by the arteriosclerotic process or by thrombosis, that the incidence of pain doubled." These authors did not mention the exact incidence of pain in cases of thrombosis alone.

CORONARY SCLEROSIS

Sclerosis of the coronary arteries was present in varying degree in every case of our series, even in the 2 instances of rheumatic and 1 of

syphilitic heart disease. From the gross and microscopic descriptions of the vessels it was found possible to estimate roughly the amount of coronary sclerosis present in each case, grading it as mild, moderate or marked. The patient with periarteritis nodosa showed typical involvement of the coronary vessels. It was described as follows in the autopsy protocol:

> The coronary arteries had an unusual appearance. On the anterior surface of the branches which emerge from the auriculoventricular margin were seen many small translucent spherical enlargements of their walls, so that the vessels appeared to have a series of small beads or nodules. A few of the vessels on the posterior surface also showed this unusual condition.
>
> Microscopically the most striking changes in the heart were seen in the coronary vessels. The arterial walls were greatly enlarged, owing to the proliferation of young fibrous tissue in the intima, reducing the lumens to slits or obstructing them entirely. The periarterial tissue showed many young fibroblasts and was rich in capillaries. Other vessels showed organizing thrombi, in some instances the thrombi being infiltrated with many lymphocytes. The coronary arteries were thus the seat of a process typical of periarteritis nodosa.

This rather unusual case was included in the series because it answered the criterion as to the size of infarct used in selection, there being a small recent infarct at the apex of the left ventricle, measuring about 1 cm. in diameter, with a mural thrombus beneath it. The walls of the larger vessels were thickened, but no thrombosis was present on gross examination. The high incidence of pain in the presence of actual thrombosis plus acute infarction will be discussed later. At this point it may be noted that there was no pain in this case, although an acute infarct was present and thrombi were seen in the small vessels under the microscope. Small infarcts, even though recent, when due to microscopic thrombi probably do not cause pain, possibly because the smaller arteries are almost devoid of sensory nerves.

In group 1, 13 patients (22 per cent) showed a mild to moderate degree of coronary sclerosis, and 45 (78 per cent) showed marked sclerosis. In group 2, moderate involvement was noted in only 5 patients (12 per cent) and advanced coronary sclerosis in 37 (88 per cent). Of 18 patients in the two groups showing only a mild or moderate degree of coronary sclerosis, 13 (72 per cent) suffered from pain, and 5 (28 per cent) did not. Of a total of 82 patients showing marked coronary sclerosis, 37 (45 per cent) did not have pain, as against 45 (55 per cent) who did show this symptom. Thus pain seems to occur more frequently in the presence of a mild or moderate degree of vascular sclerosis than it does in the advanced stages. With maximal grades of sclerosis, pain may be present or absent in approximately an equal number of cases. One cannot draw any definite deductions from these figures other than to state that the presence or absence of pain does not directly vary with the degree of sclerosis.

Although some of the factors which have been discussed seem to bear a definite relation to the pain of coronary occlusion, no single one is found which offers a complete explanation of the mechanism of pain production. However, as will be shown later, the action of a combination of several of these factors sheds more light on this problem.

COMMENT

Clinical interest in the origin of cardiac pain may properly be said to have begun with the classic observation of William Harvey, who showed his sovereign, Charles I, that the heart itself is "without a sense of touch." [15] The demonstration was made on a man whose thoracic wall had been partially removed by accident. After the first correct clinical diagnosis of cardiac infarction, by Hammer,[16] the excellent thesis of Marie [17] and the description of the syndrome by Obrastzow and Straschesko,[11] there appeared the first comprehensive study of the disease in this country, by Herrick.[18] Since 1912 numerous American observers have established the various clinical features of this condition, emphasizing severe precordial, substernal or epigastric pain as a cardinal feature. In recent years there has been a gradual, although not general, recognition of the fact that coronary occlusion is often unassociated with pain. Isolated case reports do not afford an index as to the actual frequency. The published reports of groups of cases bearing on this point place the incidence at from 38 to 61 per cent. Of our series of 100 patients studied post mortem, painless coronary occlusion occurred in 42 per cent.

From the preceding analysis one can roughly visualize two main types of coronary disease which lead to cardiac infarction. The first type, present in a somewhat larger group of patients than the other, is characterized clinically by painful seizures, tending to occur somewhat earlier in life and bearing no sexual preference except that the peak mortality is reached a decade sooner in males than in females. The patients afflicted with pain are more likely to have a previous history of stenocardia, preceding hypertension is more common, dyspnea is usually overshadowed in severity by pain and a pericardial friction rub is much more frequent. At autopsy this group of patients is

15. Harvey, W. The Works of William Harvey, translated by R. Willis, London, Sydenham Society, 1847, p. 383.

16. Hammer, A.: Ein Fall von thrombotischen Verschluss einer der Kranzarterien des Herzens, Wien. med. Wchnschr. **28**:97-102, 1878.

17. Marie, R.: L'infarctus du myocarde et ses conséquences, Thesis, Paris, no. 88, 1896.

18. Herrick, J. B.: Clinical Features of Sudden Obstruction of the Coronary Arteries, J. A. M. A. **59**:2015 (Dec. 7) 1912.

more likely than the other group to show acute infarction of the heart, acute pericarditis and actual thrombosis of a larger coronary vessel. The location of the infarct and the occurrence of hemopericardium due to rupture of the ventricle have no relation to pain. Painful infarcts are more likely to occur in the presence of mild or moderate sclerosis than are painless ones.

The second group of patients, somewhat smaller than the first, show clinical absence of cardiac pain. Attacks tend to occur later in life, with no relation to sex except that males appear to die a decade earlier than females. Preceding thoracic pain and hypertension are less common than in the first group, while dyspnea is more often a dominant symptom. A pericardial friction rub is rarely heard in cases of painless occlusion. At autopsy the hearts of these patients tend to show old infarcts, absence of acute pericarditis and relatively fewer instances of thrombosis of the coronary arteries. The location of the infarct and the presence of hemopericardium secondary to ventricular rupture bear no relation to the absence of pain. This group of patients shows relatively few instances of mild or moderate sclerosis of the coronary arteries. Marked sclerosis is about as frequent in this group as in the first.

It is evident that no single factor of those analyzed will enable one accurately to differentiate the painful from the painless type of coronary occlusion. Our study does suggest, however, that in the first group of patients, with painful occlusion, one is dealing with a rather more acute process in which relatively sudden obstruction of a coronary artery by (1) a thrombus tends to result in (2) acute cardiac infarction and (3) acute pericarditis. If one reviews the entire series of 100 cases with the idea of discovering a combination of factors, rather than a single one, which bear a more direct relation to pain, it is found that 15 patients showed actual thrombosis accompanied by acute infarction and that 10 of these also had acute pericarditis. Every one of these 15 patients had painful occlusion. On the other hand, our study suggests that painless coronary occlusion represents a more gradually developing pathologic process, in which (1) the progressive narrowing of the artery results from fibrosis rather than from actual thrombosis, and that this in turn appears to lead as a rule to (2) old fibrous infarcts with (3) rather infrequent acute pericarditis. In the entire series there were 17 patients with old cardiac infarcts who had no record of thrombosis or of acute pericarditis. Twelve of these 17 patients (70 per cent) did not have pain, while 5 (30 per cent) did show this symptom. It is possible that 1 or more of the 5 patients who had pain may have had thrombi in the vessels which were not discovered. It is well recognized [6] that thrombi in the coronary arteries may be overlooked unless numerous cross sections are made and the vessels are

carefully examined. Reexamination of hearts already studied proves that, in spite of reasonable care, this lesion may be missed. Furthermore, the pain suffered by all these patients was relatively mild, and dyspnea was an outstanding symptom in 4 of them.

If one again refers to table 2, with the thought that perhaps a combination of factors rather than a single one may bear some more definite relation to cardiac pain, one finds the following interesting facts:

1. The 5 patients with acute infarction unaccompanied by pain showed no evidence of thrombosis.

2. Six of the 11 patients with old infarction accompanied by pain revealed either acute pericarditis or thrombosis. The remaining 5 patients with old infarction and with pain may have had thrombi which were overlooked. Furthermore, pain was of slight degree in every instance and was overshadowed by dyspnea in 4.

3. Of 8 patients with acute pericarditis without pain, 6 showed no thrombosis, while the other 2 had marked sclerosis of the coronary arteries.

4. In each of the 13 patients with painless occlusion with actual thrombosis, marked sclerosis was present.

5. Twenty of the 25 patients with painful occlusion without thrombosis showed acute infarction or acute pericarditis. The 5 remaining patients with pain but no thrombosis were the same 5 with old infarction mentioned under paragraph 2. Actual thrombosis may have been present in some of these cases, and the pain of mild degree was overshadowed by dyspnea in 4 of them.

6. In each of the 5 patients with painless occlusion with mild or moderate sclerosis there was absence of thrombosis.

THEORETIC CONSIDERATIONS

The manner in which cardiac pain is initiated in coronary occlusion has been explained in various ways, as reviewed in detail by Sutton,[19] Katz [20] and Wiggers.[21] Of the several explanations, the theory most widely accepted today is that of Lewis,[22] who advanced the idea that the pain is dependent on myocardial ischemia. He stated that impairment of the coronary circulation results in disturbance of the nutrition

19. Sutton, D. C.: Cardiac Pain, J. A. M. A. **97**:1369-1370 (Nov. 7) 1931.

20. Katz, L. N.: Mechanism of Pain Production in Angina Pectoris, Am. Heart J. **10**:322-327, 1935.

21. Wiggers, C. J.: The Physiology of Cardiac Pain, in Levy, R. L.: Disease of the Coronary Arteries and Cardiac Pain, New York, The Macmillan Company, 1936, chap. 6, pp. 163-180.

22. Lewis, T.: Pain in Muscular Ischemia: Its Relation to Anginal Pain, Arch. Int. Med. **49**:713-727 (May) 1932.

of the cardiac muscle and the rapid development of an unknown chemical "P substance" which acts as a pain-producing stimulus to the nerve endings. This theory has been supported by Herrick,[23] who has explained one of its most obvious defects, viz., its failure adequately to account for the absence of pain in a large percentage of cases, even though extreme grades of ischemia are present. He has stated that in gradually progressive coronary sclerosis, ischemia may result in an area that is "relatively anesthetized by destruction of vessels, nerve and functioning muscle, so that a painful response to the new obstruction is lacking. The final complete obstruction comes without a sudden shock, the element of surprise is lacking as the heart is in a sense prepared for the supreme insult."

It is well known that the cardiac muscle itself is insensitive to pain on mechanical stimulation and that the afferent sensory fibers which do respond to such stimuli lie in the adventitial layers of the coronary arteries and send terminal branches at intervals to the smooth muscle fibers of the arterial coat, the richness of the nerve supply increasing toward the base of the heart.[24] In any discussion of cardiac pain this fact is of prime importance. The fundamental question is whether the sympathetic nerve endings in the blood vessels are stimulated by a chemical substance resulting from ischemia alone or whether they may also respond to pure mechanical stimulation. The source of the pain in either case is in the wall of the coronary vessel and not in the cardiac muscle per se. It seems logical to suppose, therefore, that sclerotic changes in the coronary arteries must bear some direct relation to the presence and absence of pain in coronary occlusion. One might further suppose that early atheromatous changes in the walls of the coronary arteries render the afferent nerve endings hypersensitive to painful stimuli, so that slight changes in the tension within the affected vessels would produce pain just as readily as would a hypothetic chemical substance. Further, it is conceivable that advanced sclerosis of the coronary vessels may lead to actual degeneration of the nerve endings in the vascular wall or that stiffening of the arterial coat and loss of elasticity may reach a point at which a sudden change in tension is no longer an adequate stimulus to the production of pain. Whether the stimulus is chemical or mechanical, however, pain must be initiated by a factor acting on the sensory nerves in the adventitial or muscular coats of the coronary arteries.

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23. Herrick, J. B.: Coronary Artery in Health and Disease, Am. Heart J. **6**: 589-607, 1931.

24. Katz, L. N.; Mayne, W., and Weinstein, W.: Cardiac Pain: The Presence of Pain Fibers in the Nerve Plexus Surrounding the Coronary Vessels, Arch. Int. Med. **55**:760-772 (May) 1935. Moore, R. M., and Singleton, A. O., Jr.: Peripheral Course of Pain Fibers Supplying Coronary Arteries and the Myocardium, Proc. Soc. Exper. Biol. & Med. **32**:1492-1494, 1935.

From a physiologic point of view it is logical to believe that afferent nerve fibers of blood vessels may respond to mechanical as well as to chemical stimuli. In a normal blood vessel, occlusion of the lumen is accompanied by pain, provided the distention of the wall of the vessel is sufficient to reach the threshold level of pain. If the obstruction is sudden the pain may be intense. Embolism of the femoral artery, e. g., after operation, is generally attended by severe pain, but gradual fibrotic narrowing of the same artery leading to marked ischemia may occur without pain. Dissecting aneurysm of the aorta is characterized by excruciating pain, which is directly associated with the stretching and tearing of the arterial wall. By analogy there is a strong argument that the mechanical factor of tension is important in the mechanism of pain production in arteries.[25] In coronary occlusion it is suggested that pain varies directly with the speed with which increased tension is produced on the wall of the coronary artery proximal to the obstruction and with the pathologic changes in the wall of the vessel, whether these changes are due to reduced elasticity or actual degeneration of the sensory nerves.

The mechanical theory of cardiac pain has been suggested many times in the past, but an imposing majority of physiologists and cardiologists at present favor the explanation of cardiac pain on the basis of ischemia [22] or anoxemia.[26] The studies of Wenckebach,[27] however, and more recently those of other observers submit evidence in support of a mechanical theory. Herrmann [2d] said: "In personal experimental studies I have noted distention of the artery behind the obstruction, and this led me to express the idea that it is the dilatation of the artery and the consequent stretching of its wall, proximal to the obstruction, that causes the stimulation of the nerve plexus about the vessel and the initiation of pain." Allbutt [28] concluded that a similar mechanism accounts for cardiac pain by causing tension on the aorta. Against the mechanical theory of cardiac pain, the argument has been advanced that occlusion of a coronary vessel can have no significant effect on the arterial pressure within it.[29] While the argument that the tension

25. The work of Bray (Bray, H. A.: Tension Theory of Pleuritic Pain, Am. Rev. Tuberc. **13**:14-20, 1926) in showing that pleural pain is due not to friction rub but to tension on the nerve endings in the parietal pleura, stimulated our interest in the problem of cardiac pain.

26. Keefer, C. S., and Resnik, W. H.: Angina Pectoris: A Syndrome Caused by the Anoxemia of the Myocardium, Arch. Int. Med. **41**:769-807 (June) 1928.

27. Wenckebach, K. F.: Toter Punkt, "second Wind," und Angina pectoris, Wien. klin. Wchnschr. **41**:1-6, 1928.

28. Allbutt, T. C.: Diseases of the Arteries Including Angina Pectoris, New York, The Macmillan Company, 1915.

29. Wiggers, C. J., and Cotton, F. S.: Studies on the Coronary Circulation: I. The Coronary Pressure Pulses and Their Interpretation, Am. J. Physiol. **106**: 9-15, 1933.

factor may cause cardiac pain appears physiologically sound, the evidence which we have thus far presented does not disprove Lewis' concept of the role of myocardial ischemia in the production of cardiac pain. Our study does suggest, however, that a mechanical as well as a chemical factor may initiate the pain in coronary occlusion. Further, it affords an apparently reasonable explanation for the total absence of pain in certain cases of cardiac infarction, in which extreme grades of ischemia proved by autopsy are present.

It is fully realized that the factor of tension in the production of cardiac pain must be subjected to carefully controlled experimental studies before its significance can be appreciated. Added evidence of its importance has been obtained by showing that cardiac pain may be produced in animals by tension on the walls of the coronary arteries alone and without a significant disturbance of the circulation of blood in these vessels, or, in other words, that pain may be initiated without ischemia.[30]

SUMMARY

Study of the clinical histories and necropsy data for 100 patients with proved coronary occlusion showed that 58 had cardiac pain and 42 did not, indicating a higher frequency of painless occlusion than is generally recognized.

The following broad statement may be made regarding group 1, comprising 58 patients who suffered from cardiac pain in a fatal attack: The patients tend to be younger, males show the peak mortality ten years earlier than do females, a history of preceding attacks of anginal pain and of hypertension is more common, pain overshadows dyspnea as a symptom and a pericardial friction rub is much more often heard. Actual thrombosis, acute infarction, acute pericarditis and milder grades of coronary sclerosis are more frequently encountered than in the patients in group 2. The location of the infarct and the rupture of the ventricle, with resulting hemopericardium, bear no relation to pain.

The following general statement may be made regarding group 2, comprising 42 patients who had no pain in a fatal attack of coronary occlusion. The patients tend to be older than those in group 1, males show the peak mortality a decade earlier than do females, a history of preceding attacks of anginal pain and of hypertension is less common, dyspnea is generally an outstanding symptom and a pericardial friction rub is rarely heard. Old infarcts, with absence of actual thrombosis and pericarditis, are more frequent. Marked sclerosis of the coronary

30. Martin, S. J., and Gorham, L. W.: Cardiac Pain: An Experimental Study with Reference to the Tension Factor, Arch. Int. Med., this issue, p. 840.

arteries is slightly though not significantly more often encountered. The location of the infarct and the rupture of the ventricular wall, with resulting hemopericardium, bear no direct relation to the absence of pain.

A combination of actual thrombosis of the coronary artery and acute infarction was accompanied by pain in every one of the 15 instances in which these two factors were present. A combination of fibrotic narrowing of a coronary artery, without actual thrombosis, plus old infarction and absence of pericarditis was not accompanied by pain in 12 of 17 patients (70 per cent). All the 5 patients who did have pain suffered from only a slight degree of it; dyspnea was the dominant symptom in 4 of these cases.

The old mechanical theory of cardiac pain advocated by Allbutt and Wenckebach and more recently advocated by Herrmann, which has been generally discarded in favor of Lewis' theory of ischemia, has been reexamined in the light of our study, and the role of a tension factor has been emphasized. Briefly, according to this theory the pain in coronary occlusion varies directly with the speed with which increased tension is produced on the wall of the coronary artery proximal to the obstruction and with the pathologic changes in the wall, whether these changes are due to a reduced elasticity or an actual degeneration of the sensory nerves.

The tension factor seems to offer a reasonable explanation not only for the presence but for the absence of pain in cases of coronary occlusion.

Added support for the importance of the factor of tension in the production of cardiac pain has been obtained by an experimental study on animals, the results of which are recorded in a separate communication.

CARDIAC PAIN

AN EXPERIMENTAL STUDY WITH REFERENCE TO THE TENSION FACTOR

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Cardiac pain has long been of clinical interest, but not until the past decade has it been subjected to laboratory investigation. Although Allbutt's [1] theory of the aortic origin of angina pectoris was once widely accepted, recent experimental evidence strongly points toward the cardiac origin of pain. Sutton and Lueth [2] have shown that compression by means of a ligature on coronary vessels in the unanesthetized dog results in pain characteristic of angina pectoris. Their studies have been confirmed by White, Garrey and Atkins [3] and by Katz and his associates.[4] All these authors have agreed that the fundamental mechanism initiating pain is a chemical factor produced by impaired coronary circulation. In essence, this contention is the basis of Lewis' [5] theory that myocardial ischemia is the cause of cardiac pain. From the aforementioned studies it is generally inferred that the mechanical factor is of secondary importance in producing cardiac pain.

That the mechanical or tension factor may be of major significance has been expressed by Herrmann [6] and has been suggested in a recent

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From the Department of Physiology and Pharmacology and the Department of Medicine, Albany Medical College, Union University.

1. Allbutt, T. C.: Diseases of the Arteries Including Angina Pectoris, New York, The Macmillan Company, 1915.

2. Sutton, D. C., and Lueth, H. C.: Pain, Arch. Int. Med. **45**:827-867 (June) 1930.

3. White, J. C.; Garrey, W. E., and Atkins, J. A.: Cardiac Innervation: Experimental and Clinical Studies, Arch. Surg. **26**:765-786 (May) 1933.

4. Katz, L. N.; Mayne, W., and Weinstein, W.: Cardiac Pain: The Presence of Pain Fibers in the Nerve Plexus Surrounding the Coronary Vessels, Arch. Int. Med. **55**:760-772 (May) 1935.

5. Lewis, T.: Pain in Muscular Ischemia: Its Relation to Anginal Pain, Arch. Int. Med. **49**:713-727 (May) 1932.

6. Herrmann, G. R.: Synopsis of Diseases of the Heart and Arteries, St. Louis, C. V. Mosby Company, 1936, p. 214.

clinicopathologic study of painful and painless coronary occlusion.[7] The following experiments have been performed in an effort to determine the possible importance of a mechanical factor in the initiation of cardiac pain.

PROCEDURE

Seven normal adult dogs were prepared under pentobarbital sodium anesthesia and artificial respiration, which are essential according to the procedure of Sutton.[8] The significant modification of this author's technic employed in our experiments was the use of four or five ligatures, instead of one or two, placed as follows: In the first animal a black silk ligature was looped through the visceral pericardium and the adventitia of the wall of the anterior descending branch of the left coronary artery on its right side about 2 cm. from its aortic opening. A second ligature was then similarly introduced into the left side of the wall of the same vessel (fig. 1 *A*). Care was taken not to pass the ligatures into the lumen of the vessel. In the remaining 6 dogs three ligatures were inserted in like manner, but each was placed approximately 90 degrees from its neighbor and in the same transverse plane (fig. 1 *C*). This modification was carried out in order to preserve the coronary blood flow and at the same time to permit the application of tension (fig. 1 *D*). In these dogs, in addition, a fourth ligature was passed under the same vessel and through the myocardium about 1.5 cm. distal to the initial ligatures, and, finally, a fifth or control ligature was put through the visceral pericardium and myocardium a few centimeters to the right or to the left of the same coronary artery. These ligatures were then led to the exterior of the thoracic cage through separate flanged glass tubes that were sewed in place in the parietal pericardium, with the proximal ends of the tubes extending freely into the pericardial cavity (fig. 2). In 3 cases a sixth ligature was attached to the parietal pericardium and extended to the surface of the chest. The rest of the surgical procedure was completed in the manner previously described,[2] and the dogs were permitted to recover from the anesthesia.

RESULTS

The criteria accepted as signifying the presence of pain in dogs awakening from anesthesia were, in general, similar to those reported by Sutton and Lueth.[2] In order, there occurred in 80 per cent of the observations (1) an initial and rapid increase in heart rate; (2) an initial temporary decrease in the rate of respiration, with marked increase in amplitude, followed by dyspnea and tachypnea; (3) movements of the legs, characteristically first the left foreleg, then the right hindleg and finally all four extremities; (4) extension of the head and neck, and (5) last, a gasping inspiratory whine. Salivation was noted in only 33 per cent of the observations. No animals were allowed to suffer. Application of tension on the coronary ligatures was terminated

7. Gorham, L. W., and Martin, S. J.: Coronary Occlusion With and Without Pain: Analysis of One Hundred Cases in Which Autopsy Was Done with Reference to the Tension Factor in Cardiac Pain, Arch. Int. Med., this issue, p. 821.

8. Sutton, D. C., and King, W. W.: Physiological Effects of Temporary Occlusion of the Coronary Vessels, Proc. Soc. Exper. Biol. & Med. **25**:842-844, 1928. Sutton and Lueth.[2]

as soon as the pain response was noted. In all animals the sensitivity to ordinary painful stimuli on recovery from the anesthesia was determined as a control. The stimuli used consisted of pinching the skin of the groin with a hemostat, passing a needle through the skin and also incising the skin of this area with a scalpel.

A. Effect of Tension on the Ligatures in the Coronary Artery.—1. Preliminary tests, made by exerting a steady, firm pull on the ligatures, were performed on all dogs before the parietal pericardium was closed by suture. The results were as follows: (*a*) Marked tension on any one of ligatures 1 to 4, inclusive (fig. 2 *A*), or simultaneously on the lateral ligatures (1 and 2 in dog 1 and 1 and 3 in all others)

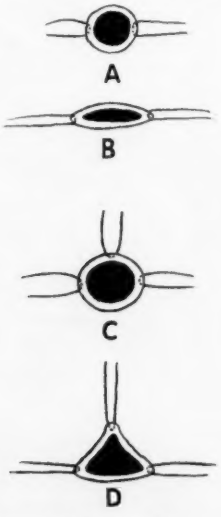

Fig. 1.—Sketch showing the position of the ligatures in the coronary artery. *A*, the right and left lateral ligatures. *B*, the ligatures are the same as those in *A* except that there is tension on them. *C*, ligatures 1, 2 and 3 are approximately 90 degrees apart and in the same plane. *D*, the ligatures are the same as those in *C* except that there is tension on them.

produced flattening and blanching of the distal portion of the coronary vessel. This compression of the vessel and the resulting pallor of the distal portion of the artery signified not only the satisfactory and secure position of the ligatures but also the probable complete cessation of the coronary blood flow. (*b*) Moderate or mild tension on these same ligatures caused no change in color or contour of the vessel distally except in the case of ligature 4. In the case of this ligature, which encircled the vessel, the results were uniformly similar to those recorded under *a*, since even mild tension resulted in a marked decrease of blood

flow. (*c*) Mild to marked tension applied equally and simultaneously to ligatures 1, 2 and 3 produced no visible change in either the color or the contour of the vessel distally. It may be reasonably inferred, therefore, that the coronary blood flow was not seriously impaired (fig. 1 *D*). (*d*) Tension of varying degrees on ligature 5 of course had no effect on the coronary artery. It resulted only in elevating a portion of the myocardium and in increasing the heart rate.

2. In the series of dogs used, after recovery from anesthesia, four to six hours later, it was observed that the sensitivity of the skin to painful stimuli varied. The threshold of pain was definitely lowered by the anesthesia, since none responded to pinching of the skin in the groin or the passing of a needle through it. However, all but 1 dog reacted to the stimulus of the cutaneous incision in varying degree,

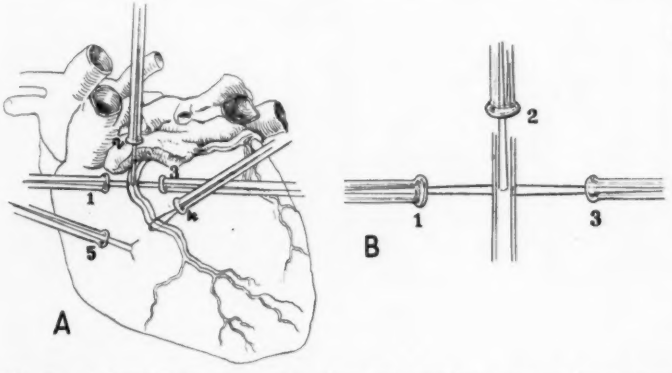

Fig. 2.—*A* showing five ligatures in place and extending from the heart through flanged tubes. *B*, a diagrammatic representation of the position of coronary ligatures 1, 2 and 3.

characterized chiefly by movement of one or both hindlegs and an increase in the cardiac and respiratory rates. There was no dyspnea. Movement of the forelegs, extension of the head and neck and the gasp-like inspiratory whine, which so definitely characterize pain produced by tension on the coronary vessel, were all absent.

The observations made when tension was applied to the different ligatures are summarized in table 1. It can be readily seen from this table that tension for less than half a minute on any one of ligatures 1 to 4 or on any combination of them initiated cardiac pain in the unanesthetized dog. There was also a notable decrease in the rate of respiration, with a compensatory increase in amplitude. Tension for four minutes on the myocardium and visceral pericardium by means of ligature 5 or, in 3 cases, the ligature on the parietal pericardium produced only a rise in heart rate but none of the significant features

of cardiac pain. This observation confirms previous reports.[9] With reference to respiration, the changes were slight. The onset of pain seemed to occur earliest by the simultaneous pulling of ligatures 1, 2 and 3 and latest on tension of a single ligature. The time required for the return to normal of the cardiac and respiratory rates and for the disappearance of other signs of cardiac pain was significantly prolonged when tension was exerted on ligature 4 (under the coronary vessel). According to the generally accepted theory of ischemia, this may have been due to the time necessary for the removal of the accumulated metabolites resulting from complete coronary occlusion.

TABLE 1.—*Summary of Data on the Application of Tension on Ligatures in the Coronary Arteries of Seven Unanesthetized Dogs*

Number of Observations	Ligature Under Tension	Normal*		Tension of Ligatures (Approximately 5 Gm.)					Application of Tension After Change in Heart Rate, Seconds	Average Onset of Pain, Seconds	Average Return to Normal, Seconds
		Heart Rate per Min.	Respiratory Rate per Min.	Average Increase in Heart Rate per Min.	Average Initial Decrease in Respiratory Rate per Min.	Movement of Legs	Extension of Head	Cry†			
38	L_1 or L_2 or L_3	158	38	32 (20-43)	9.0 (6-14)	+	+	±	15-25	35 (30-44)	51 (39-62)
27	L_1 and L_3	166	40	28 (18-35)	6.5 (4-9)	+	+	+		34 (26-42)	65 (56-80)
34	L_1 L_2 L_3 Simultaneous	153	36	33 (22-34)	8.5 (7-12)	+	+	+		23 (18-37)	40 (36-52)
29	L_4	165	37	35 (14-44)	8.0 (6-11)	+	+	+		33 (26-40)	71 (59-87)
26	L_5	159	32	27 (12-37)	±1.5	0	0	0	240	0	29 (15-37)

* Four to six hours postoperatively and after recovery from the anesthesia. No artificial respiration was used.

† A whining cry was noted in only 80 per cent of the observations recorded as indicating pain.

In determining the time for both the onset and the duration of pain, all five of the aforementioned criteria were taken into consideration. This accounts for the unduly prolonged intervals in the initiation of pain. However, if only the gasping, whining cry was considered as evidence of pain, its appearance and disappearance were noted within intervals of twenty seconds. Further, the cry was heard significantly earlier when tension was applied simultaneously to ligatures 1 to 3 than when applied to ligature 4 (surrounding the artery).

It must be emphasized that tension on any one or any two of the first three ligatures resulted in a direct mechanical stimulation of the coronary afferent nerve and possibly also in a chemical one, owing to

9. Sutton and Lueth.[2] Katz, Mayne and Weinstein.[4]

some impairment in coronary flow. Tension on ligature 4, which encircled the vessel, similarly might initiate pain, owing to both chemical and mechanical stimuli. However, with equal and simultaneous tension on ligatures 1, 2 and 3 there was only mechanical stimulation. The patency of the lumen was maintained, no ischemia resulted and hence no chemical stimulus was possible. Direct observation of the effect of tridirectional tension on the wall of the vessel by ligatures 1, 2 and 3 was made in every experiment before the pericardial cavity was closed. In no instance could any decrease in the volume of coronary blood flow be seen with the naked eye. Further proof, however, of the functional integrity of the coronary flow to the cardiac muscle under these conditions was sought and obtained by the electrocardiographic studies, which will be presented later.

3. Blocking of stimuli by local application of alcohol was then attempted. In 2 of the dogs the procedure just cited was repeated after a few drops of 80 per cent alcohol was placed successively over the various ligatures. Application of tension on ligatures 1, 2 and 3 when alcohol was dropped over only ligature 4 gave rise to a typical pain response; however, no pain was initiated when ligature 4 or 5 was pulled on for several minutes. In like manner, no evidence of pain could be elicited by means of tension on ligatures 1, 2 and 3 after application of alcohol over these ligatures. The stimuli for cardiac pain, therefore, can be blocked by local application of alcohol whether they are initiated by a chemical or by a mechanical factor. This is in agreement with previous reports.[9]

B. Determination of the Minimal Threshold of Tension.—The minimal amount of tension on the ligatures in the coronary artery necessary to invoke a pain response was determined in 4 unanesthetized dogs prepared in the manner described. The ligatures were passed over a pulley and attached to varying weights exerting a vertical pull. The results obtained are given in table 2 and show that pain was initiated with a minimum tension produced by a 7 Gm. weight applied to any one of the first four ligatures. With a 10 or 15 Gm. weight the pain was greater and seemed to appear sooner. Five gram weights were ineffective when applied to any single ligature. In the case of ligature 5 (through the myocardium) a 25 Gm. weight failed to elicit a pain response even after three minutes. When equal tension was applied simultaneously to ligatures 1, 2 and 3, marked pain was noted with the successive use of 15 and 7 Gm. weights attached to each ligature, moderate pain with 5 Gm. weights, mild but definite pain with 3 Gm. weights and, in 1 dog only, suggestive pain with 2 Gm. weights. No pain was noted in any dog when 1.7 Gm. weights were used. One dog failed to show this pain response with a 3 Gm. weight on each of the first three ligatures but responded in characteristic fashion when 5 Gm. weights were employed.

It is fully appreciated that, from the few observations made, little can be concluded as to the exact amount of tension necessary to produce pain. Further, one cannot ignore the variation in response noted, which of course might easily be greater if a larger series of animals were studied. However, it nevertheless appears of remarkable interest that in some dogs, at least, mechanical tension on the wall of a coronary artery equivalent to 3 Gm. on each of ligatures 1, 2 and 3 can, without impairing the coronary flow of blood, elicit the response of cardiac pain.

C. Electrocardiographic Studies.—The preliminary tests of applying tension simultaneously on the first three ligatures, with the animal anes-

TABLE 2.—*Minimal Threshold of Tension Initiating Cardiac Pain in Four Unanesthetized Dogs*

Number of Observations	Ligature Under Tension	Weight, Gm.	Pain Response*	Average Onset of Pain, Seconds
19	L_1 or L_2 or L_3	5	0	
		7	+	40
		10	++	35
34	L_1, L_2, L_3 Simultaneous	15	+++	24
		7	+++	29
		5	++	38
		3	+ ±	37
		2	±	42
		1.7	0	
29	L_4	15	+++	32
		7	+	39
		5	0	
23	L_5	15	0	
		25	0	

* 0 indicates no pain; +, mild pain; ++, moderate pain; +++, marked pain.

thetized and the thoracic cage and pericardium open, showed that no change in color or contour of the distal region of the coronary artery and, of course, no pain response occurred. With the pericardial and thoracic cavities closed and the dog recovering from the anesthesia, several hours later, a repetition of the tests elicited in all cases the typical response of cardiac pain. It was tentatively concluded, though not fully proved, that no functional impairment in the coronary flow resulted and, therefore, that the only possible stimulus to the coronary afferent nerves was a mechanical one. During the course of the investigation Blumgart and his associates [10] reported that experimental occlusion of the anterior descending branch of the left coronary artery in cats revealed within thirty seconds a characteristic elevation of the ST wave of the electrocardiogram. We had already made use of the electro-

10. Blumgart, H. L.; Hoff, H. E.; Landowne, M., and Schlesinger, M. J.: Experimental Studies on the Effect of Temporary Occlusion of Coronary Arteries in Producing Persistent and Electrocardiographic Changes, Am. J. M. Sc. **194**: 493-502, 1937.

cardiogram in our dogs to determine significant impairment in coronary blood flow and functioning myocardium. Proof that pain was produced without circulatory change in the muscle and hence without a chemical stimulus appears to have been established by the electrocardiographic studies now to be described.

The control and the later experimental electrocardiograms were all taken while the dogs were under pentobarbital sodium anesthesia. This precaution was necessary, since otherwise tension on the ligatures caused cardiac pain and resulted in marked movements of the body. In order to prove that these animals retained their sensitivity to pain after recovery from anesthesia, the experiments with application of tension to the various ligatures were all repeated. Typical responses of cardiac pain again were noted in every case.

Leads I to IV were taken in every case in the following order: (1) on the day preceding the experiment, to serve as a control record; (2) after surgical preparation of the animal; (3) after the application of tension (15 Gm.) simultaneously on each of ligatures 1, 2 and 3 for twelve minutes; (4) after similar tension was applied for twelve minutes on ligature 5 (through the myocardium), and (5) after tension on ligature 4 (surrounding the vessel) for two to three minutes.

Electrocardiograms taken in all cases the day preceding the experiment were entirely normal. The significant changes from normal after the experimental procedures were carried out may be briefly summarized as follows:

1. Immediately after surgical preparation there was sinus tachycardia, and the T wave was inverted in lead III in all cases; the T wave was also inverted in leads I and II in dogs 4 and 5.

2. After simultaneous tension on ligatures 1, 2 and 3 or after tension on ligature 5 there was sinus tachycardia; the T wave was occasionally upright in lead II, but in most of the cases it was inverted in leads I and III. Electrocardiograms made after surgical preparation and application of tension on ligatures 1, 2 and 3 (attached to the vessel wall) or ligature 5 (inserted in the myocardium) were essentially the same and were, with the exception of changes in the T wave in leads I and II, approximately normal.

3. After tension on ligature 4, which surrounded the artery, for forty to seventy seconds, there was sinus tachycardia again, with occasional premature beats and elevation of the ST segment in lead IV in many beats.

4. After tension on ligature 4 for two or three minutes, in addition to observations noted under paragraph 3, the ST segment was elevated in leads I to III; P was upright in lead IV; Q was absent in lead IV and T was wide and notched in leads II and III; the T wave occasionally was diphasic in lead IV. The electrocardiogram made after the appli-

cation of tension on ligature 4 was typical of the electrocardiograms in cases of coronary occlusion. Figure 3 shows the electrocardiographic changes observed for a single animal (dog 4) after the various procedures just detailed.

D. Pathologic Studies.—In order to determine the precise location of the ligatures in the wall of the coronary artery, all the animals were studied post mortem. It was noted grossly that no ligature was torn out of place as a result of the application of tension and no hemorrhage had resulted. At the time the ligatures were implanted, no serious bleeding was observed in any of the animals. It was therefore tenta-

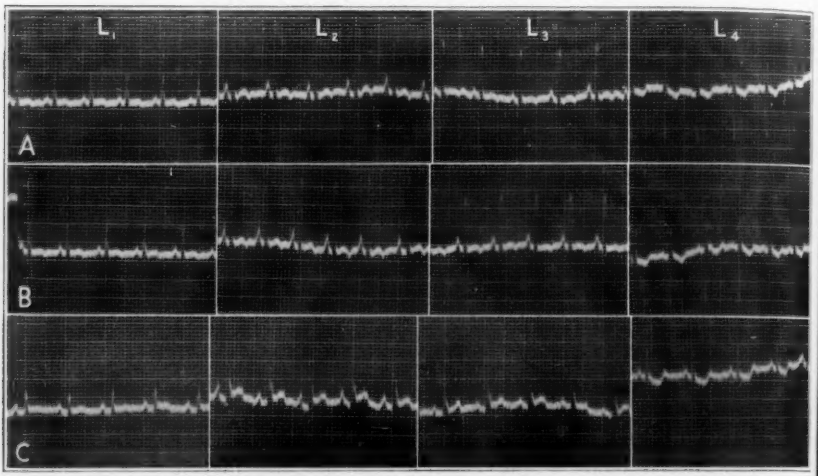

Fig. 3.—A series of electrocardiograms made (*A*) after surgical preparation of dog 4, (*B*) after postoperative application of tension simultaneously on coronary ligatures 1, 2 and 3 for twelve minutes and (*C*) after application of similar tension on ligature 4 for two and one-half minutes. Electrocardiograms *A* and *B* are essentially the same and, with the exception of changes in the T wave in leads I and II, are normal. *C* is typical of the electrocardiograms obtained in cases of coronary occlusion.

tively concluded that the lumens of the coronary arteries had not been pierced or torn.

Tissues from the heart were fixed in Bouin's fluid, and serial sections through the sites of the ligatures were prepared for microscopic study, hematoxylin and eosin stains being employed. Over six hundred serial cross sections were examined. In none of them was there any evidence of frank hemorrhage or of penetration or rupture of the arterial wall at any point. Surrounding the implanted silk ligatures in most cases, signs of an early acute inflammatory reaction were noted. Because of

the difficulty in sectioning tissues with embedded silk thread, it was not easy to prepare sections showing all three ligatures in position without distortion, as the thread tended to be torn out. Figure 4 *A*, however, represents a cross section of the descending branch of the left coronary

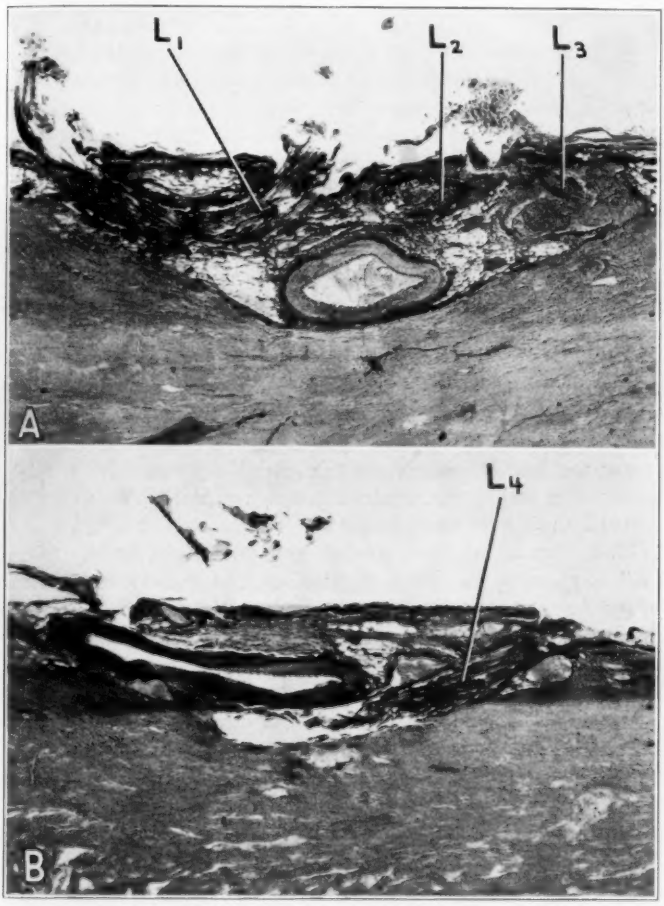

Fig. 4.—*A*, cross section of the descending branch of the left coronary artery of dog 4, showing the position of ligatures 1, 2 and 3 in adventitial tissue and in the same plane. *B*, another photomicrograph of the same artery, showing the position of ligature 4 underneath the vessel.

artery with ligatures 1, 2 and 3 in the adventitial tissue. In some instances ligature 1 or 3 passed through the adjacent myocardium as well as through the adventitia. The position of ligature 4, underneath

the coronary artery, can readily be seen in figure 4 *B*. Both photomicrographs show that the continuity of the arterial wall was intact. In no instance was there evidence of injury to any part of the vessel.

COMMENT

The perception of pain is admittedly a nervous phenomenon dependent essentially on the presence and integrity of the proper receptors and their afferent pathways. With regard to cardiac pain, recent investigations have established the importance of the sympathetic afferent nerves [3] in the coronary adventitia and surrounding connective tissue [4] and their ipsilateral pathway to the spinal cord.[11] In man and in the monkey the parietal pericardium is similarly innervated, while the myocardium and visceral pericardium are devoid of afferent nerves. In the dog both pericardial layers as well as the myocardium per se are insensitive.[12] In the absence of visceral pericardial nerves, true cardiac pain in man, in the monkey and in the dog can arise only from stimulation of the afferent nerves surrounding the coronary vessels.

The natural question arises, What actually stimulates these afferent nerves? or, more properly, What factors initiate the nervous impulses? According to the prevalent theory of myocardial ischemia,[5] impaired coronary circulation results in an abnormal accumulation of naturally occurring metabolites, one or more of which, perhaps lactic acid in particular, may irritate chemically the pain receptors. This concept is supported by many investigations.[13]

With acceptance of the statement that lactic acid, or the "P substance," is an adequate chemical stimulus, the question still remains unanswered as to how this substance, produced in the cardiac muscle, is transferred from its site of origin to the coronary afferent nerves to exert its action. Does the lactic acid, or "P substance," in the myocardium flow back upstream to reach the coronary adventitia and the branches of the nerve supply, or, more correctly, is the accumulation of lactic acid, or "P substance," in the wall of the vessel responsible for the initiation of pain? One may ask more logically, Why may not these receptors in the coronary arteries, like pain receptors elsewhere in the body, be subject to mechanical as well as chemical stimulation?

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11. Moore, R. M., and Singleton, A. O., Jr.: Peripheral Course of Pain Fibers Supplying Coronary Arteries and the Myocardium, Proc. Soc. Exper. Biol. & Med. **32**:1492-1494, 1935.

12. Sutton and Lueth.[2] Katz, Mayne and Weinstein.[4] Moore and Singleton.[11]

13. Himwich, H. E.; Goldfarb, W., and Nahum, L. H.: Changes of the Carbohydrate Metabolism of the Heart Following Coronary Occlusion, Am. J. Physiol. **109**:403-408, 1934. Katz, L. N.: The Mechanism of Pain Production in Angina Pectoris, Am. Heart J. **10**:322-327, 1935. Wiggers, C. J.: The Physiology of Cardiac Pain, in Levy, R. L.: Diseases of the Coronary Arteries and Cardiac Pain, New York, The Macmillan Co., 1936, chap. 6, p. 177. Sutton and Lueth.[2]

The modified technic of Sutton [2] has afforded an opportunity to investigate the probable importance of the mechanical factor in initiating cardiac pain. It is believed that adequate care has been exercised to eliminate the chemical stimulus. Our experiments showed that cardiac pain was experienced by unanesthetized dogs by means of simultaneous tridirectional tension on the wall of the coronary artery. That there was no material impairment of the coronary blood flow under these conditions was evidenced by the absence of electrocardiographic changes. We feel convinced that the mechanical or tension factor in the absence of a chemical one can be an effective stimulus for producing cardiac pain. Shambaugh [14] has shown that the pain response can be elicited in dogs if the aortic blood pressure is suddenly increased in the presence of subminimal constriction of the coronary vessels. The epinephrine used to produce the rise in aortic blood pressure also dilates the coronary vessels. This sudden dilatation may, in itself, mechanically stimulate the onset of pain. When elasticity is reduced, as in a sclerosed vessel, tension may be minimized, and painless coronary occlusion may be expected.[7]

Our experiments do not offer any direct evidence to disprove the possibility of the generally accepted theory that ischemia is the cause of cardiac (coronary) pain, but they do prove that pain may be produced mechanically in the absence of any chemical stimulus. The proponents of the theory of ischemia, on the other hand, have not yet demonstrated experimentally that pain can be produced by a chemical stimulus alone in the absence of any mechanical factor.

The onset of cardiac pain caused by simultaneous tension on ligatures 1, 2 and 3 (lying in the adventitia) is much quicker than that caused by tension on ligature 4, which surrounds the coronary artery. The intensity of the pain is greater also in the first instance even though the pull exerted is approximately the same. These facts may possibly be explained by supposing that a more effective stimulus is evoked by ligatures placed in the nerve-bearing adventitia than can be aroused by a ligature encircling the entire vessel. The cessation of pain is more prompt on release of the three ligatures inserted in the wall of the vessel than it is when the artery is both occluded and pulled by ligature 4.

Although the minimal threshold of tension necessary to initiate cardiac pain was determined, it is at best only approximate and holds true only for the dog. Further, the method used to determine the degree of tension necessary is subject to criticism in that the variation in the pressure in the coronary artery, the more natural mechanical stimulus, has not been estimated. This fact is thoroughly appreciated and will be investigated in subsequent studies.

14. Shambaugh, P.: Circulatory Changes in Angina Pectoris: An Experimental Study, Arch. Int. Med. **56**:59-76 (July) 1935.

SUMMARY

An attempt has been made to determine the role of the mechanical factor in the initiation of cardiac pain in dogs recovering from anesthesia. It has been found that a typical pain response can be elicited when tridirectional tension in one plane is applied to a coronary vessel in such a manner as to cause no change in blood flow. With this procedure the chemical factors caused by impaired coronary blood flow are completely eliminated, as shown by the absence of changes in the electrocardiogram. The minimal threshold of tension on ligatures in the coronary vessel was 3 Gm. in the series of dogs used. Local application of alcohol can block stimuli initiating cardiac pain, whether mechanical or chemical in origin. It is concluded that tension alone on the coronary arteries in dogs may serve as an adequate stimulus for the initiation of cardiac pain.

Dr. Arthur W. Wright, of the Department of Pathology, cooperated by preparing the histologic material used in this study. Miss M. L. Smith and Miss A. P. Schafer were of technical assistance in the preparation of the illustrations.

COCCIDIOIDES INFECTION (COCCIDIOIDOMYCOSIS)

II. THE PRIMARY TYPE OF INFECTION

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Ever since coccidioidal infection has been known to be due to a fungus,[1] it has been recognized that there are two distinct cycles of development of the infecting organism: the form which occurs when the organism has infected animal tissues, and the one which occurs when the organism grows on culture medium and, presumably, in nature. The first of these cycles was that observed when infected human beings came under clinical observation. The parasitic organism was seen as a double-contoured spherule, averaging about 30 microns in diameter, which reproduced by endosporulation, the endospores being released into the tissues by rupture of the wall of the mother spherule. The spherules so closely resembled Coccidia that it was at first believed that they belonged to the protozoan group, and they were called Coccidioides, i. e., like Coccidia; hence the name. The second cycle occurs when the organism grows outside the body, the vegetative stage; and here it appears as a white moldlike fungus which reproduces by the formation of chlamydospores. The chlamydospores are numerous and light and are easily transported in the air, particularly when associated with dust.

Since the earliest studies of the disease coccidioidal granuloma, there has been great interest in how the infection is acquired by man and, much more recently, by certain domestic animals, viz., cattle and sheep. As early as 1905 Ophüls [2] wrote concerning a case which occurred in California in 1900, "These observations prove the occurrence of primary

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The study of coccidioidomycosis is being aided by the Rosenberg Foundation, San Francisco.

From the Department of Public Health and Preventive Medicine, Stanford University School of Medicine, San Francisco, and the Kern County Department of Public Health, Bakersfield, Calif.

1. Ophüls, W., and Moffitt, H. C.: A New Pathogenic Mould (Formerly Described as a Protozoan: Coccidioides Immitis Pyogenes), Philadelphia M. J. **5**:1571, 1900.

2. Ophüls, W.: Further Observations on a Pathogenic Mould Formerly Described as a Protozoon (Coccidioides Immitis, Coccidioides Pyogenes), J. Exper. Med. **6**:443, 1900-1905.

pulmonary infection in this disease, very probably due to inhalation of the parasitic organism which causes it." In 1929 Ophüls still held the opinion that inhalation of chlamydospores is an important factor, for when discussing the papers by Cummins, Smith and Halliday and by Pulford and Larson, he said:[3]

> For the mode of infection, all evidence so far gathered seems to point to respiratory involvement with a primary localization of the virus in the lung. In almost all cases that have come to autopsy, it is possible to find an old primary focus in the lungs, and the pulmonary lesions are often of great clinical and pathologic importance. The infecting agent is evidently the spore which develops on the aerial hyphae of the mycelium of the fungus. It is probably the spores of the fungous growth that becomes mixed with dust and are then inhaled into the lungs. The finding of the disease in animals such as cattle and sheep does not seem to me to suggest that the infection is from animals to human beings. It is much more likely that the animals contract the disease much in the same way as human beings do in the infected region.

The majority of workers, however, have apparently disregarded the fact that in the vegetative stage of growth the fungus Coccidioides reproduction is accomplished by means of chlamydospores and have had their attention focused on the endospores, which are seen exclusively when the organism has become involved in its parasitic phase. Since prolonged observation has failed to show any person to person or animal to person infection, there has been nothing to show how this disease may be transmitted, if one fails to remember that the chlamydospores of the vegetative stage may be responsible for the primary infection. Various possible methods of transmission, even including transmission by insects,[4] as in tularemia or Rocky Mountain spotted fever, have been suggested, but none has been proved to be adequate.

Unquestionable proof that inhalation of chlamydospores of the fungus Coccidioides will cause infection of human beings was given by the case of a young man who became infected in the laboratory of the Department of Public Health and Preventive Medicine at Stanford University Medical School. His case was mentioned in a previous report in the ARCHIVES OF INTERNAL MEDICINE[5] and more fully discussed later in *California and Western Medicine*.[6] In the latter report 4 other cases were cited in which the patients had acquired their illness

3. Ophüls, W., in discussion on Cummins, W. T.; Smith, J. K., and Halliday, C. H.: Coccidioidal Granuloma, J. A. M. A. **93**:1046 (Oct. 5) 1929. Pulford, D. S., and Larson, E. E.: Coccidioidal Granuloma, ibid. **93**:1049 (Oct. 5) 1929.

4. Jacobson, H. P.: Fungus Diseases, Springfield, Ill., Charles C. Thomas, Publisher, 1932, p. 213.

5. Dickson, E. C.: Coccidioides Infection: Part I, Arch. Int. Med. **59**:1029 (June) 1937.

6. Dickson, E. C.: "Valley Fever" of the San Joaquin Valley and Fungus Coccidioides, California & West. Med. **47**:151, 1937.

in the San Joaquin Valley and were typical cases of the "valley fever" or "desert fever" of that district. This disease has been recognized frequently in the San Joaquin Valley, but so far as we can learn had not hitherto been described in the medical literature. The first time it was mentioned in an official publication was in the annual report to the county supervisors by the Kern County Department of Public Health for 1935-1936, where it was described as San Joaquin fever.

The frequency of the disease is indicated by replies to a questionnaire which was mailed on May 15, 1937, to physicians who were practicing in eight counties of the San Joaquin Valley. They were asked how many cases of San Joaquin fever or erythema nodosum had been recorded since Jan. 1, 1936. Of 127 physicians who replied, 52 reported that they had recorded no cases during that time, but 75 reported that they had

Cases of Valley Fever Recorded by Seventy-Five Physicians in the San Joaquin Valley, Calif., from Jan. 1, 1936, to May 15, 1937

	Fresno	Kern	Kings	Madera	Merced	San Joaquin	Stanislaus	Tulare	Totals
Number of doctors reporting cases	19	10	7	6	4	12	7	10	75
Number of cases reported	69	117	24	31	11	29	18	55	354
Males	27	48	6	9	4	15	5	25	139
Females	42	69	18	22	7	14	13	30	215
Fever	68	117	17	30	11	27	15	52	337
Cough and sputum	19	48	6	22	1	4	9	15	124
Recovery without complication	65	115	20	31	11	15	17	51	325
Progressed to typical coccidioidal granuloma	..	1	..	..	..	..	..	..	1

recorded 354 cases up to May 1937. The accompanying table shows in what counties these 75 physicians were located and that the occurrence of cases was recognized in all parts of the San Joaquin Valley, although more frequently in the southern counties. For instance, 263 of the 354 cases were reported from Fresno County and the counties south of Fresno.

It was found that valley fever occurs at all seasons of the year. Of the cases reported in the answers to this questionnaire, 32 per cent had their onset in the spring, 23 per cent in the summer, 25 per cent in the autumn and 20 per cent in the winter. Both sexes were affected; 138 cases (39 per cent) were in males and 216 (61 per cent) were in females. Persons of all ages were included: 3 per cent were children of preschool age, 18 per cent were children of school age, 51 per cent were young adults and 28 per cent were persons over 40. It is particularly interesting that all 354 patients but 1 recovered without complications after an illness of a few weeks. In 1 patient coccidioidal meningitis developed and was fatal.

The onset of the acute illness is often spoken of at first as a bad cold or "flu." Usually the patient complains of feeling ill, with headache and often with general body aches and pains. Some complain especially of aches and pains about the chest, as in pleurisy, and some of indefinite gastrointestinal disturbance. Frequently there is a history of mild sore throat, which is sometimes attributed to tonsillitis. Occasionally there is some conjunctivitis, with hyperemia of the scleras but with nothing suggestive of phlyctenules. Fever may begin at the time of onset of symptoms or four or five days later, after distress in the upper respiratory tract has attracted attention. Not infrequently the temperature is not higher than 100 to 101 F., but sometimes, usually later, when signs of bronchopneumonia appear, it may be 104 or even 105 F. Once in a while a patient has an early chill, and some complain of sweating; but chills and sweats are not constant.

There is usually bronchitis, sometimes with unproductive cough, but varying amounts of sputum are common. It appears that cough and the production of sputum occur relatively early and often cease after a few days. At times the sputum is produced in considerable amount and may be streaked with blood. Often the patient improves after a few days' illness and feels that he is getting better, but in from eight to fifteen days after the onset, erythematous nodules develop on the skin; these are described popularly as bumps. The lesions are typically those of erythema nodosum in most cases, but sometimes have the appearance of erythema multiforme.

The erythema nodosum usually appears primarily on the shins, where the nodules are most numerous. Not infrequently they may occur on the thighs, sometimes on the buttocks or on the arms and occasionally in the scalp or on the upper portion of the thorax, producing a collar-like arrangement around the root of the neck. The lesions do not fluctuate or suppurate but may be fiery red and so tender or painful that the weight of the bedclothes may be disagreeable. At other times they are merely hypersensitive. Within from forty-eight to seventy-two hours they begin to turn purplish and fade, and in four or five days they have usually disappeared except for a brownish pigmentation, which may persist for weeks after the tenderness and swelling have disappeared. Occasionally, but rarely, there may be a successive crop of erythema nodosum after an interval of three or four weeks.

The temperature usually subsides gradually after the "bumps" disappear (fig. 1), and usually there are no recurrences. The leukocyte count usually ranges from normal to about 15,000, but the differential count often shows eosinophilia. The highest eosinophil count which we have seen was 8 per cent on the day the "bumps" first appeared, which

increased to 13 per cent five or six days later and then dropped to 2 per per cent. In 1 case in which there were two crops of erythema nodosum about four weeks apart, there were 10,800 leukocytes, with 7 per cent eosinophils, with the first attack and 5,500 leukocytes, with 5 per cent eosinophils, at the time of the second attack. In the interval between the two outcroppings the eosinophil count was not higher than 2 per cent. In another case, one in which there was no erythema nodosum, the patient suffered pains in the wrists and ankles at the time

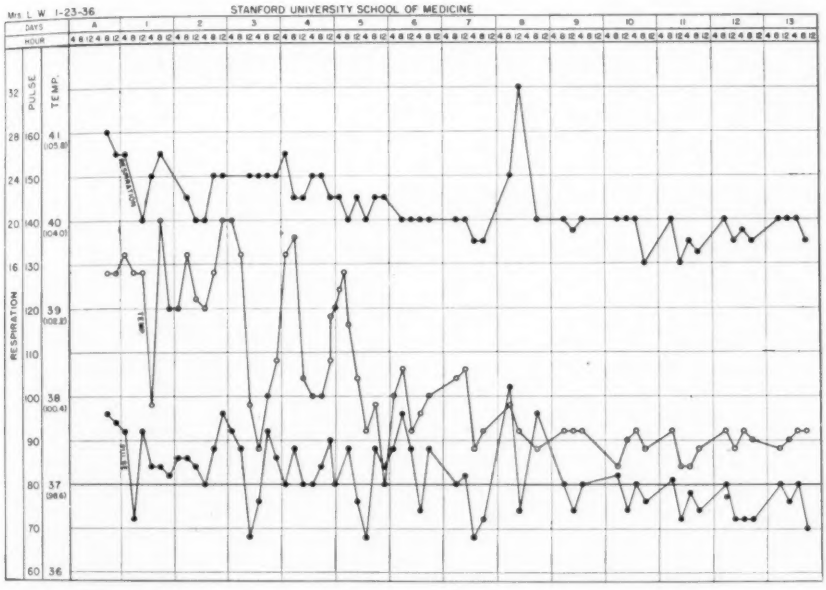

Fig. 1.—Temperature chart. The patient had valley fever and entered Stanford University Hospital at the time erythema nodosum appeared.

the erythema nodosum might have been expected, and during that period there were 8 per cent eosinophils.

A diagnosis of valley fever is seldom if ever made before the erythema nodosum is present; in fact, the presence of erythema nodosum is one of the manifestations on which the diagnosis depends. It is the tenderness or pain in the erythematous lesions, the so-called bumps, which brings many of the patients under medical attention. It is said that a large percentage of patients never seek medical attention at all, particularly if the erythematous lesions are not painful; and it is known that some patients infected with Coccidioides have an

illness which is diagnosed as "flu" or have more or less severe pneumonia without the occurrence of erythema nodosum. Consequently, it is often said that there is no sputum when the patient comes under medical observation, although there may be a history of some cough with sputum at the beginning of the acute attack. In reply to the questionnaire in which 354 cases of valley fever were reported, of only 174 was it stated that there were cough and sputum at the time of erythema nodosum; but at the Stanford University laboratory forty-three specimens of sputum from patients with valley fever have been received for examination, of which thirty-six contained Coccidioides. Most of the sputums containing Coccidioides were collected between from six to twenty days after the date given as that of the onset of acute illness, but there was 1 case in which the sputum still showed the fungus after two months. Specimens from patients in hospitals in San Francisco showed the fungus when collected from seventeen to thirty days after the onset of illness. It should be remembered that for children who are too small to raise sputum, gastric lavage is necessary, as in early tuberculosis. In 1 such case the washings obtained by gastric lavage contained mucopurulent material in which were sporulating and nonsporulating spherules of Coccidioides. Pure culture of the fungus was obtained from the mucopurulent material, and guinea pig inoculation proved that it was a virulent Coccidioides. It was also found that the coccidioidal spherules were soon digested out by the acid gastric secretion.

The laboratory diagnosis of Coccidioides from a study of the sputum is not difficult if one but remembers to look for the spherules. Characteristic spherules may be seen in fresh cover slip preparations in many instances. All that is necessary is to study the fresh unstained specimen under a microscope, with the illumination cut down, as for examination of urinary sediment for casts. Plain spherules or spherules with endospores may be seen, the double-contoured capsules being distinct with a low degree of illumination. It should be remembered that the spherules average about 30 microns in diameter. Stained smears are less satisfactory than fresh cover slip preparations, because the spherules are likely to be distorted during the process of drying and fixing. The fungus grows readily on ordinary culture mediums, but for diagnostic purposes Sabouraud medium is preferable. Growth of the fungus usually appears in from forty-eight to seventy-two hours, but a culture should not be called sterile until at least a full week of incubation has elapsed. The colony appears as a white fungous growth, which gradually enlarges until it may be 1 inch (2.5 cm.) or more in diameter when on an agar plate. It consists of white, finely branched mycelium.

For differential diagnosis of the fungus and to establish its virulence, it is necessary to inject the fungus into a guinea pig. If male animals are selected and intraperitoneal injections are given, it will be found that the testicles enlarge, as in glanders, within two or three weeks. When the animal is killed, in about one month or six weeks, there is extensive involvement in the organs of the peritoneal cavity, often in the lungs, in the omentum and in the regional lymph glands, as well as in the testicles. Pus from the lesions shows many sporulating and nonsporulating spherules of Coccidioides. By intratesticular injection

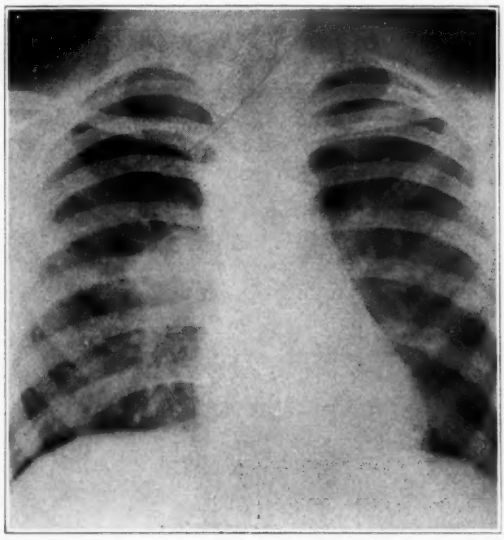

Fig. 2.—Roentgenogram of a patient with valley fever in the Kern County Hospital, Bakersfield, Calif. Coccidioides was recovered from the sputum.

the time necessary for identification of the spherules in pus from the testicles may be reduced to from ten to fourteen days.

If roentgen examination of the chest is made at the time the erythema nodosum appears, opacities in the pulmonary shadows are seen which have often been described as indicating tuberculosis (fig. 2). For instance, concerning the first patient who was observed, a young man who was infected in a laboratory, Dr. W. E. Chamberlain, then at Stanford University Medical School, wrote in his report of Sept. 19, 1929:

Roentgenographically there seems to be massive involvement of the upper lobe of the right lung with tuberculosis; lobar pneumonia is, of course, a possibility

from the roentgenographic standpoint, but my impression is that the clinical picture rules out pneumonia and makes tuberculosis the much more likely explanation.

On October 17, approximately one month later, Dr. Chamberlain reported:

The abnormal densities in the left lung have entirely disappeared. The abnormal densities in the upper lobe of the right lung are considerably more than half gone; there remains just a trace of the former mottling and consolidation in the caudal portion of the upper lobe.

In another case, that of a 24 year old man who was admitted to Kern County Hospital, in Bakersfield, Calif., the following roentgenographic report was made: "A differential diagnosis between a bilateral exudative type of tuberculosis and bilateral bronchopneumonia with interlobar empyema of the right side must be made." A subsequent roentgenogram of the chest, four and a half months after his discharge from the hospital, showed both lungs clear. Typical Coccidioides, proved virulent by guinea pig inoculation, was recovered from the sputum in both of these cases.

Similar reports have frequently been made by many roentgenologists who have examined patients with so-called valley fever. The typical picture includes evidence of enlargement of the hilar glands, branching shadows from the hilar region of the lungs and more or less scattered areas of shadows indicating involvement of the parenchyma of the lung, in either the upper or the lower lobes. Signs of pleurisy, pleurisy with effusion or interlobar empyema may be seen at times.

It is characteristic in the great majority of cases of acute coccidioidomycosis that when roentgen examination of the chest is made from one to several months after the acute illness, it is found that the earlier pulmonary lesions, which appeared so similar to those of tuberculosis, have entirely disappeared and the lungs are described as clear (figs. 3 and 4).

Use of coccidioidin is particularly valuable in the diagnosis of valley fever. Coccidioidin is a specific antigen used in making cutaneous tests. It was first recognized by Davis,[7] in 1924, and later studied by Hirsch and Benson,[8] da Fonseca and de Arêa Laëo[9] and Jacobson.[10]

7. Davis, D. J.: Coccidioidal Granuloma, with Certain Serologic and Experimental Observations, Arch. Dermat. & Syph. **9**:577 (May) 1924.

8. Hirsch, E. F., and Benson, H.: Specific Skin and Testis Reactions with Culture Filtrates of Coccidioides Immitis, J. Infect. Dis. **40**:629, 1927.

9. da Fonseca, O., and de Arêa Leão, A. E.: Réaction cutanée spécifique avec le filtrat de cultures de Coccidioides immitis, Compt. rend. Soc. de biol. **97**:1796, 1927.

10. Jacobson, H. P.: Coccidioidal Granuloma: Specific Allergic Cutaneous Reaction; Experimental and Clinical Investigations, Arch. Dermat. & Syph. **18**: 562 (Oct.) 1928.

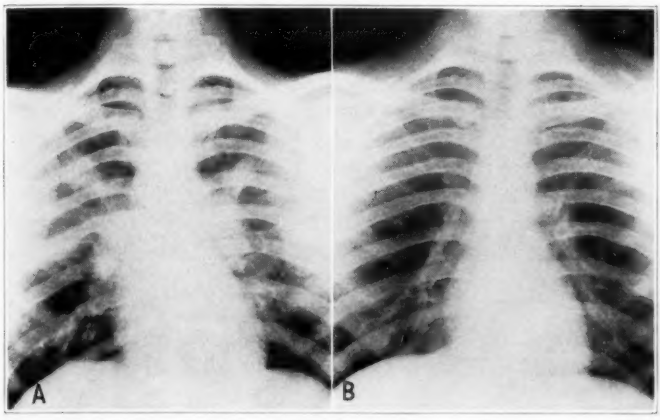

Fig. 3.—Acute infection with Coccidioides (valley fever). The sputum showed Coccidioides. *A*, roentgenogram taken at the Kern County Hospital, Bakersfield, Calif., on July 29, 1936. *B*, roentgenogram taken on Dec. 14, 1936.

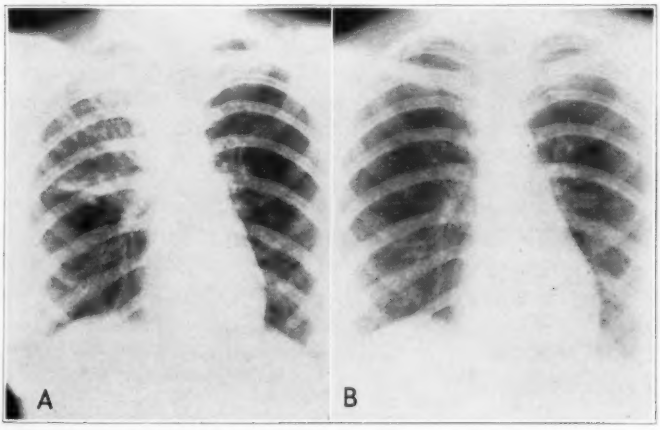

Fig. 4.—Acute infection with Coccidioides (valley fever). The sputum showed Coccidioides. *A*, roentgenogram taken at the Kern County Hospital, Bakersfield, Calif., on March 9, 1937. *B*, roentgenogram taken on Oct. 14, 1937.

It was described by Jacobson [4] as the filtrate of a broth culture of Coccidioides which has been incubated from ten to thirty days and then passed through a Berkefeld filter. Kessel [11] modified this by grinding a portion of the mycelium of the culture and adding it to the broth before filtration. The method of use is the same as the Mantoux method of testing with tuberculin. Jacobson reported that for general diagnostic work for infection with Coccidioides, 0.1 cc. of the filtrate is injected intracutaneously and if a positive reaction is obtained the characteristic local area of erythema is produced, which reaches its maximum intensity, often with some vesiculation, in about forty-eight hours. The lesion produced begins to fade in a few days and usually has disappeared in from eight to fourteen days, but local pigmentation of the skin may persist for a variable time thereafter.

The length of time after infection that sensitization of the patient may occur is not known, but in guinea pigs and rabbits which have been infected by inhalation of chlamydospores, the coccidioidin tests first give a positive reaction six or seven days after the inoculation. The length of time the sensitization lasts is also unknown; but persons who have been examined ten years after having valley fever have shown a strongly positive reaction to coccidioidin, although they had shown no indication of coccidioidal lesions since the occurrence of valley fever and were apparently entirely free from them at the time of examination.

Patients who are suffering from valley fever, the initial acute infection of the respiratory tract with the chlamydospores of Coccidioides, react acutely to the coccidioidin test. It has been found that with some lots of coccidioidin the intracutaneous injection of 0.1 cc. may produce a severe reaction or even local necrosis of the skin in some cases. It has therefore been found desirable to use diluted coccidioidin, up to 1:1,000 dilution of some specimens, for the initial test. With a specimen of coccidioidin which we are using at present, it has been found that for the initial test it is preferable to use 0.1 cc. of 1:1,000 dilution, followed if necessary by 0.1 cc. of 1:100 or of 1:10 dilution. It should be emphasized that it is necessary to use a syringe and needle which have not been used for tuberculin, as otherwise the reaction may be confusing if the patient shows a positive reaction to the tuberculin test.

It is unfortunate that up to the present no method for standardization of coccidioidin has been perfected, and it is impossible to predict its potency except by clinical trial. The active antigenic substance has not been identified. The closest laboratory method of standardization is to study the comparative reaction in infected guinea pigs or rabbits,

11. Kessel, J. F.: Personal communication to the authors.

but there is so little known about variations in the intensity of the infection and the possibility of varying degrees of sensitivity to different intensities of the infection that at present the differences in the reaction of laboratory animals is not satisfactory for standardization of material to be used on human beings.

The incidence of valley or desert fever, that is, the incidence of cases in which the initial symptoms resembled influenza, or "flu," bronchitis and sometimes pleurisy or bronchopneumonia, followed by an outbreak of erythema nodosum, is high in the San Joaquin Valley. The demonstration that the great majority of specimens of sputum from patients with valley fever have been shown by culture and guinea pig inoculation to contain virulent Coccidioides indicates that the majority if not all cases of valley fever are caused by infection with Coccidioides. And the fact that the great majority of patients with valley fever survive without apparent complications proves that infection with Coccidioides is not, in all stages of the disease, the highly fatal disease which it has been believed to be. From 1894 to July 1937, 495 cases of coccidioidal granuloma were reported in California, with 249 deaths; therefore, the mortality from coccidioidal granuloma in California has been practically 50 per cent. However, the great majority of patients with valley fever survive; among the 354 patients in the series mentioned, only 1 showed coccidioidal granuloma and died. Hence, the mortality rate of patients who acquire infection with Coccidioides is extremely low. The actual mortality rate cannot be estimated until there are accurate data concerning the actual incidence of cases of the preliminary acute infection.

But it has been found in a number of cases of acute infection with Coccidioides that erythema nodosum has not developed; therefore, these cases have not been included in the group of cases of valley or desert fever; usually or often the condition is classified as "flu." In a number of such cases Coccidioides has been recovered from the sputum, but the percentage of such cases is not known. However, in the cases in which coccidioidal granuloma has developed some have been noted in which there was no history of erythema nodosum, as well as cases in which there was a history of such an illness. The incidence of valley fever, therefore, does not indicate the total incidence of acute infection with Coccidioides.

REPORTS OF CASES

The following brief abstracts of case histories indicate the various types which have been discussed. The first group of 5 were of the type in which a diagnosis of valley fever was made, that is, cases in which erythema nodosum was present.

CASE 1.[12]—A white farm laborer aged 23 had been exposed to dust in Kern County while harrowing. He had lived in Kern County for three months. On Dec. 6, 1936, a severe cold developed, with pains in the chest. During the following two weeks he felt ill and had a small amount of tenacious sputum. On December 18 a rash developed which simulated rose spots on the arms and lower portion of the abdomen, but this was entirely cleared within three days. On December 24 he had erythema nodosum on the legs, from the knees down. The lesions were tender, reddened "bumps," which he described as being "sore as a boil."

Roentgen examination of the chest showed a feathery infiltration of the parenchyma of the lungs and considerable hilar adenopathy. The sputum contained typical spherules of Coccidioides. The leukocyte count was 17,850, with 2 per cent eosinophils. The coccidioidin test gave a strongly positive reaction; a well marked bleb and edema developed, with an erythematous area measuring 25 by 35 mm. in diameter.

After a troublesome illness the patient became afebrile and apparently recovered completely. On Sept. 3, 1937, a roentgenogram showed that both pulmonary fields were entirely clear.

CASE 2.[12]—A white woman aged 41 had been picking cotton in Kern County, where she had lived for seven months. She complained that the cotton was dusty. On Dec. 24, 1936, she complained of fever, pains in the chest, cough and soreness throughout both sides of the chest. She entered the Kern County Hospital on January 4, where a diagnosis of infection of the upper respiratory tract was made. She left the hospital on January 12, against her physician's advice, because she was feeling so much better. On January 14 reddened, tender, swollen "bumps" developed on the anterior and posterior surfaces of the legs and on the thighs. The roentgenogram of the chest taken on January 25 showed increased density in the right hilar region, with small projections extending into the pulmonary fields. The coccidioidin test showed a central bleb, measuring 20 by 25 mm., surrounded by a hyperemic area, measuring 80 by 100 mm.

The leukocyte count was 6,850, with 78 per cent polymorphonuclear neutrophils. Culture of the sputum showed growth of a white mold, and on guinea pig inoculation infection with Coccidioides was produced. The patient recovered.

CASE 3.—A white boy aged 3½ years was brought to the Stanford University Hospital from Tulare County on April 13, 1937. His mother said he had had fever for two weeks and painful red nodules on the shins for two days. On March 27 he had become irritable and complained of sore throat. His temperature was 100 F., and it was considered that he had a cold. For a time there was constipation, with cramps in the bowels. The fever continued, and a few days after the onset the temperature ranged between 103 and 104 F. At this time there was a so-called heat rash on the trunk and neck, which lasted for one or two days. Two days before his admission to the hospital red, painful nodules appeared on the shins, lower portion of the thighs and buttocks which reached their maximum intensity within forty-eight hours and then began to fade. The child had become apathetic, had slept poorly and had had "night cries" for about four days before entry. A diagnosis of valley fever had been made by the local physician in Tulare County.

12. This patient was treated in the Kern County Hospital, and the case was included in the annual report of the Kern County Department of Public Health, 1936-1937.

On physical examination nothing unusual was detected except the lesions on the lower extremities, the buttocks, the extensor surface of the right forearm and just above the left elbow. The nodules were warm, red and purplish red, indurated and tender but not painful; they were discrete or confluent. On the shins they were up to 3 cm. in diameter, but elsewhere they were not larger than 1.5 cm.

A tuberculin test gave a negative reaction, but the coccidioidin test gave an extremely positive reaction, so marked that for a time local necrosis of the skin was feared. The blood count showed 8,200 leukocytes, with 53 per cent polymorphonuclears and 3 per cent eosinophils. The sedimentation test was rapid—31 mm. in sixty minutes.

Because there was no expectorated sputum, gastric lavage was done. The stomach washing contained mucopurulent material in which typical spherules of Coccidioides were seen. Culture and guinea pig inoculation proved that the diagnosis was infection with Coccidioides (fig. 5).

A roentgen examination of the chest was made on April 14, and it was reported as follows: The pulmonary roots were heavy, particularly on the left side. There was also some parenchymal infiltration on the left side at the level of the seventh and eighth ribs posteriorly. The pleura between the upper and the lower lobe was thick. In conclusion it was reported that the appearance was compatible with tuberculosis (fig. 6).

The child made an uninterrupted recovery and appeared to be well. On June 26, 1937, a second roentgenogram of the chest was reported as showing that the density in the lower lobe of the left lung had cleared remarkably, leaving only the faintest perceptible granularity in that region.

Case 4.—A white man aged 26, a medical student, was planning work with Coccidioides in a laboratory of Stanford University Medical School. On the first day, Aug. 29, 1929, that he worked with the fungus he inadvertently opened a Petri dish containing a plate culture which was several months old. He noticed a fine brownish dust rise from the culture. Undoubtedly they were chlamydospores. No other opportunity for infection was known.

On September 6, eight days later, he noticed pains in the chest, resembling the pain of pleurisy, which rapidly increased in severity. In the evening a physician could find no signs of involvement in the chest but strapped it to give relief. The temperature at the time was 99 F. For the next nine days he was far from well and tired easily. His cough became more severe, and he was obliged to spend part of his time in bed. In the morning there was much purulent sputum, which was sometimes streaked with blood. He had nearly constant headache, backache and aching in the legs. He felt that he had a fever but did not use a thermometer. On September 19 he found that he had lost 15 pounds (6.8 Kg.) in two weeks.

The patient was then confined to bed, and it was found that the temperature ranged between 99 and 100 F. A blood count showed 10,800 leukocytes, with 57 per cent polymorphonuclear neutrophils and 7 per cent eosinophils. The eosinophil count decreased in a few days to 2 per cent.

On September 25 a red, painful nodule appeared on one shin, and the next day there were several similar nodules on both shins. They were red, hot and tender and measured about 1.5 cm. in diameter. They began to subside by September 30 and on October 3 were practically gone. On November 14 there was a second crop of similar lesions on the shins, which reached their maximum size in two or three days and then disappeared. The eosinophil count at that time was 5 per cent of 5,500 leukocytes.

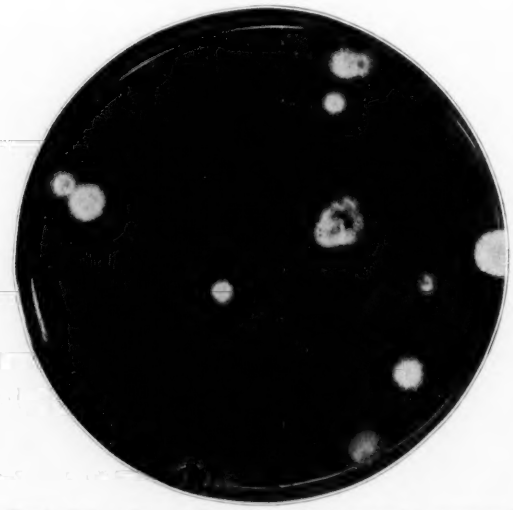

Fig. 5.—Petri dish culture of mucopurulent material recovered by gastric lavage (see fig. 6).

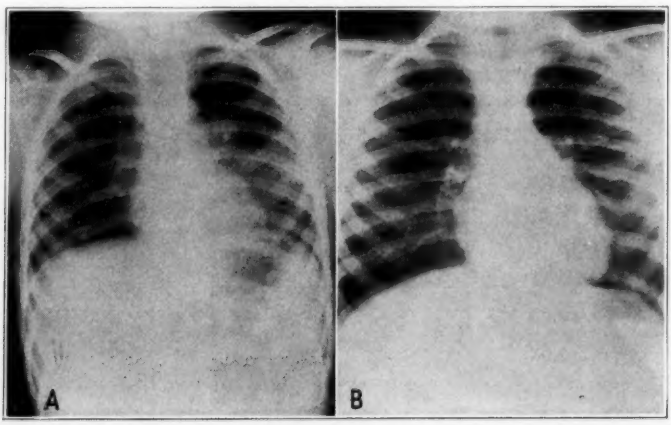

Fig. 6.—Acute infection with Coccidioides (valley fever). The sputum (see fig. 5) showed Coccidioides. *A*, roentgenogram taken on April 14, 1937. *B*, roentgenogram taken on June 23, 1937.

On November 25 his physician noted that he was progressively better. There was no cough or any other pulmonary symptoms.

The first sputum culture was made on September 24 and the last on September 27. The production of sputum ceased on that date, and no further specimens could be obtained. Examination of the sputum on September 26 showed no acid-fast bacilli. Cover slip preparations contained a moderate number of coccidioidal spherules; the majority were nonsporulating, and a few had endospores. Culture showed the characteristic fungous growth, and guinea pig inoculation resulted in typical lesions due to Coccidioides.

The roentgen examinations of the chest made on September 19 and October 17 have already been reported on. Subsequent examinations have been made frequently, and it has always been reported that the lungs were clear. The patient has been apparently well since the summer of 1930.

Comment.—The next case proves that typical acute valley fever may progress to coccidioidal granuloma and cause death.

CASE 5.[12]—A 50 year old white housewife had lived in Kern County for two months. She and her family were obliged to live in an auto camp beside a highway which was being graded and therefore were exposed to heavy clouds of dust. On Nov. 6, 1936, she had a severe cold, pleurisy and cough, with expectoration of thick, glairy, mucopurulent sputum. The thoracic symptoms improved in about three weeks, and erythema nodosum then developed, with characteristic "bumps" on the legs, thighs, forearms and hands. In December she entered Kern County Hospital, complaining of symptoms of meningitis. Repeated spinal punctures and finally trephine of the skull were performed to relieve the headaches and vomiting. The patient grew steadily weaker and died on May 13, 1937. At autopsy basilar coccidioidal meningitis was evident; culture and guinea pig inoculation of purulent exudate from the base of the brain proved that the infection was due to Coccidioides.

The white blood cell count was 12,800, with 61 per cent polymorphonuclear neutrophils. A roentgenogram of the chest taken on January 22 showed increased density of the parenchyma of the lower lobe of the left lung.

Comment.—It has already been stated that in all cases of acute primary infection with the chlamydospores of Coccidioides, erythema nodosum does not develop and therefore not all cases are classified as cases of valley fever, some being classified as cases of "flu" or bronchopneumonia. The following cases were of the latter type.

CASE 6.—A white man aged 26, a field geologist, was working on a "dusty job" in Kern County in December 1929. On December 28 he did not feel well and two days later had nausea, vomiting and diarrhea for one day, followed by constipation. On Jan. 1, 1930, he had stabbing pains in the upper left portion of the chest, but this soon subsided. The temperature was 100.5 F. He continued to feel ill and was able to work only part time. On January 9 and 10 he had aching pains in the ankles and wrists and began to cough and raise sputum. He was admitted to the hospital on January 14, complaining of pain, fever, malaise, cough and expectoration. The detailed hospital record is not available, but a diagnosis of bronchopneumonia was made. The temperature was 103.2 F. on the day of entry but was down to normal in four days. It did not rise again thereafter.

On January 14 a roentgenogram of the chest was reported as showing rather marked enlargement of the hilar glands, with slight, coarse mottling throughout the upper half of the left lung. It was concluded that the patient had tuberculosis. On January 28 another roentgenogram of the chest was reported as showing slightly less prominent markings than on the previous examination. On March 24 it was reported that the lungs were clear.

Examination of the sputum on January 27 was reported as showing no acid-fast bacilli or spherules of Oidia. On Sabouraud medium there was a fungous growth which was said to resemble that of Coccidioides. On February 21 it was reported that a guinea pig which was given an injection of the culture of the sputum showed generalized infection with coccidioidal granuloma.

It was a feature of this case that there was no erythema nodosum, but on January 7 and January 13 it was noted that there were 4 per cent and 6 per cent eosinophils, respectively, just before and after the patient complained of pains in the ankles and wrists. The patient made an uninterrupted recovery from the acute illness.

CASE 7.[13]—A Negro boy aged 15 was first seen in Fresno, Calif., on Sept. 14, 1936. About the middle of August 1936 he became ill, with chills, afternoon fever, night sweats and cough with sputum. He lost about 22 pounds (10 Kg.) in three weeks. Tuberculosis was suspected because fluoroscopic examination showed infiltration of the left lung, with the densest part near the hilus. Serial roentgenograms made in the Alameda County Hospital, to which he was referred, showed rapid clearing of the infiltration in the left lung. He remained in the hospital for two months. The sputum and stomach washings did not show tubercle bacilli, and guinea pig inoculation did not cause tuberculosis.

On December 4 the boy was seen in the clinic and said he had been feeling well and was gaining weight. Roentgen examination showed that the lung had cleared except for heavy peribronchial markings toward the base of the left lung.

On January 8 he still felt well but showed a hard, diffuse swelling on the left forearm just below the elbow. A roentgenogram showed no lesion of the bone, but by February 10 a small sinus had opened from this area. On February 19 a similar swelling was present on the left thigh just above the knee. This was fluctuant at the center, and fluid was removed by aspiration. This was proved by culture and guinea pig inoculation to contain Coccidioides.

The roentgenograms of the chest, when viewed from the standpoint of acute infection with Coccidioides, seemed to be identical with those of patients with acute valley fever (fig. 7). The maximum lesion was at or near the hilus and was associated with parenchymatous shadows, which cleared rapidly. It seems probable, therefore, that the acute onset was due to primary infection with Coccidioides, without erythema nodosum, which was followed by lesions of coccidioidal granuloma in the extremities.

CASE 8.[14]—A white man aged 41 was first seen by his physician on July 26, 1936, for acute infection of the upper respiratory tract. The physician made a diagnosis of pneumonia and sent the patient to a hospital. Bacteriologic exami-

13. Reported to us by Dr. G. E. Koerber, of Oakland, Calif.

14. This case was reported by Dr. De W. Higgs, of Chula Vista, Calif. Autopsy was performed by Dr. H. A. Ball, of the San Diego General Hospital, San Diego, Calif.

nation of the sputum showed growth of a white fungus. The patient made a fair recovery and was sent home. There was no history of erythema nodosum.

About six weeks later the patient had an acute attack, accompanied by numbness of the arms and legs and marked dizziness. For a few days he continued to work but became progressively worse and was again sent to the hospital. After a severe illness with marked mental derangement, he died in February 1937. Autopsy was performed on February 26. The anatomic diagnosis was coccidioidal granuloma with chronic basilar meningitis. The only coccidioidal lesion reported, other than those in the meninges, was a small fibrocaseous nodule, measuring slightly more than 1 cm. in diameter, in the upper lobe of the left lung. Culture could not be made because the body had been embalmed, but smears showed numerous pus cells and spherules of Coccidioides in various stages of development.

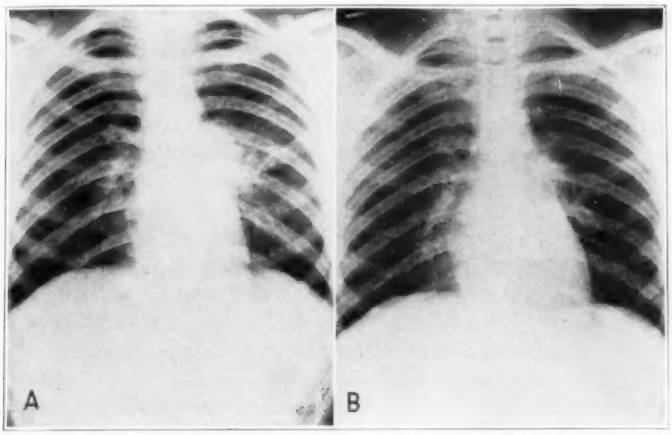

Fig. 7.—Acute infection with Coccidioides (valley fever) followed by coccidioidal granuloma. *A*, roentgenogram taken at the Alameda County Hospital, Oakland, Calif., on Sept. 17, 1936. *B*, roentgenogram taken on April 19, 1937.

COMMENT

It follows that acute primary infection with the chlamydospores of Coccidioides is of frequent occurrence in the San Joaquin Valley and usually causes a mild disease from which the great majority of victims recover without apparent complications. In a few cases coccidioidal granuloma subsequently develops when the causative organisms become disseminated by the blood stream. No attempt has been made in this report to discuss the pathology of primary infection due to Coccidioides, but it may be said that in guinea pigs and rabbits which are forced to inhale the chlamydospores of the vegetative phase of the growth of the fungus, interstitial pneumonia is produced which tends to clear promptly.

In the acute disease there is no immediate formation of tubercles, but the process is apparently limited to changes which follow the absorption of the chlamydospores by the lymphatic system. Roentgenograms of the chest of the infected animals show the same hilar and parenchymatous shadows in the lungs, which clear promptly, as those in human beings. After such a process there is marked enlargement of the peribronchial lymph nodes which drain the pulmonary field.

The reaction to inhaled chlamydospores, therefore, is a temporary irritation of the lymphatic system which does not cause immediate destruction of tissue and severe tissue damage or the production of granulomatous changes. When the chlamydospores are injected subcutaneously or into the blood stream, on the other hand, the foci of infection which are induced are typically granulomatous, and there are many spherules. Reproduction of the fungus in the parasitic phase is by endosporulation, and if the spores gain access to the blood stream they may be widely disseminated.

It is obvious that the well established name coccidioidal granuloma is not applicable to primary infection due to inhalation of the chlamydospores of Coccidioides, because the immediate reaction to such a type of infection is not to produce granulomas. It is desirable, therefore, to have some name which is applicable to all types of infection with coccidioides, whether primary or progressive (secondary).

In a previous report [6] the same coccidioidomycosis was suggested. This corresponds in form to such accepted terms as actinomycosis and blastomycosis, which indicate infection with the fungi Actinomyces and Blastomyces, respectively. Individual cases can be classified as due to primary coccidioidomycosis and progressive (secondary) or granulomatous coccidioidomycosis with further classification indicating the site of the granulomatous lesions if desired.

Such a nomenclature is somewhat cumbersome, it is true, but its use indicates recognition that there are different manifestations of infection with Coccidioides and that coccidioidal granuloma is not a disease entity but a late progressive or secondary phase of an infectious disease which is caused by the fungus Coccidioides.

SUMMARY

It has been shown that infection with the fungus Coccidioides may cause disease of a primary or secondary progressive type.

The primary form of the disease is due to inhalation of the chlamydospores formed in the vegetative phase of the growth of Coccidioides.

Infection with Coccidioides is common in the San Joaquin Valley in California; it is usually mild, and the great majority of patients recover without complications.

The condition is often diagnosed as a bad cold or "flu" in the beginning, but when erythema nodosum occurs in its course, it is popularly known in the San Joaquin Valley as desert or valley fever.

In a few cases the condition subsequently progresses to the highly fatal disease known as coccidioidal granuloma.

The name coccidioidomycosis has been suggested to include all types of infection with the fungus Coccidioides.

PULSATING ANGIOMA (GENERALIZED TELANGIECTASIA) OF THE SKIN ASSOCIATED WITH HEPATIC DISEASE

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The association of two uncommon and apparently unrelated conditions in the same patient is unusual. When this association occurs more frequently than can be explained by mere coincidence it must have some significance. Such an association was first drawn to attention when Osler [1] observed that "angiomata have a curious relationship with affections of the liver." It seems that this association is more frequent than a review of the literature indicates, and it is my purpose to draw further attention to it, review the pertinent facts and present 6 cases recently observed at the Mayo Clinic.

CHARACTERISTICS OF CUTANEOUS ANGIOMA

Though the cutaneous vascular lesions vary considerably in appearance, depending on their size, they all exhibit two essential characteristics: (1) a central angiomatous portion and (2) radiating telangiectatic vessels. The central portion varies from a bright red, punctate vascular point to a deep red, smooth, compressible elevation the size of a pea. Parkes Weber [2] was the first to note pulsation in this central eminence. In smaller lesions the radiating telangiectatic vessels may be limited to two or three fine, threadlike strands extending from 0.5 to 1 cm. from the central point. The medium-sized lesions exhibit a border, 1 to 2 cm. in width, made up of numerous radiating stellate telangiectatic vessels, producing a spider or medusa-like effect. The entire lesion may be suffused a dusky red from dilatation of deep lying vessels.

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1. Osler, W.: On a Family Form of Recurring Epistaxis, Associated with Multiple Telangiectases of the Skin and Mucous Membranes, Bull. Johns Hopkins Hosp. **12**:333-337 (Nov.) 1901.

2. Weber, F. P.: Haemorrhagic Telangiectasia of the Osler Type—"Telangiectatic Dysplasia": An Isolated Case, with Discussion of Multiple Pulsating Stellate Telangiectases and Other Striking Haemangiectatic Conditions, Brit. J. Dermat. **48**:182-193 (April) 1936.

In the largest lesions a few of the radiating vessels may assume the appearance of small, tortuous cyanotic varicosities. The smaller lesions are indistinguishable from naevus araneus, or spider nevus, seen commonly on the cheeks of children.

In most instances the lesions are limited to the skin of the head and neck, of the upper part of the chest and shoulders and of the fingers, dorsa of the hands and forearms. Occasionally they may be generalized, but in such cases most of them are in the sites mentioned. A prominent feature is the occurrence of lesions on the nasal and buccal mucosa. Slight trauma to any of the lesions, the nasal ones in particular, may give rise to alarming hemorrhage. The familial tendency which is prominent in some cases has caused the condition to become known as familial or hereditary hemorrhagic telangiectasia (Osler-Rendu-Weber syndrome).

HEPATIC DISEASE

The associated hepatic disease is usually chronic, and the findings of cirrhosis with splenomegaly preponderate. Arsenic, alcohol and syphilis are the common etiologic agents. Low grade hepatitis, splenic anemia and a malignant growth of the metastatic type have been observed. The concomitant changes in the constituents of the blood resulting from the hepatic disturbance are seen, and ascites, icterus and splenomegaly are frequent. The familial tendency observed in cases of cutaneous angioma is not so obvious in cases in which there is associated hepatic disease; van Bogaert,[3] however, has presented 2 cases of familial hepatic cirrhosis with angioma.

The relation of the time of the onset of the cutaneous lesions to that of the onset of the hepatic disease is of interest. In most cases the angiomas appear first, and frequently they antedate the hepatic disturbance by fifteen to twenty years. Usually the patient states that a few small, isolated lesions on the face or epistaxis (indicative of lesions of the nasal mucosa) was noted a number of years prior to the onset of symptoms and signs of hepatic disease. With the onset of the hepatic disease the cutaneous lesions often increase rapidly in size and number. It is not unusual to observe partial regression of the angiomas with improvement in the hepatic condition. Although difficult to prove, it seems likely, since the hepatic disease is chronic, that the damage to this organ may antedate the clinical appearance of symptoms by a long period; it is, in fact, possible that the damage might even date back to the time of the onset of the cutaneous angiomas.

3. van Bogaert, L., and Scherer, J. H.: Hémangiomatose familiale de Rendu-Osler et cirrhose hépatique; contribution à l'étude des cirrhoses familiales, Ann. de méd. **38**:290-300 (Oct.) 1935.

Data on Cases of Cutaneous Angioma (Generalized Telangiectasia) with Hepatic Disease Reported in the Literature

			Cutaneous Angiomas				Hepatic Disease				
Case	Author	Age, Yr., and Sex	Age at Onset, Yr.	Site	Pathologic Observations	Family History	Type	Age at Onset, Yr.	Icterus	Splenomegaly	Pathologic Observations
1	Osler [1]	55 M	Childhood	Face, ears, tongue, eyes and nasal mucosa	Large dilated veins	+	Carcinoma, metastatic	55	0	0	.....
2	Galloway, J.: Proc. Roy. Soc. Med. (Clin. Sect.) **4**: 42, 1911	35 M	34	Face, neck, shoulders and extremities	.....	0	Hepatomegaly, syphilitic	30	0	0	.....
3	Frick, W.: J. Cutan. Dis. **30**: 334, 1912	50 M	35	Generalized	Dilated capillaries	0	Carcinoma, metastatic	49	0	0	Carcinoma, metastatic
4	Roles, F. C., cited by Fitz-Hugh	65 F	..	Face, lips, tongue and hands	.....	0	Cirrhosis	..	0	+	.....
5	Curschmann, H.: Klin. Wchnschr. **9**: 677, 1930	54 M	..	Face, lips and palate	.....	+	Splenohepatomegaly	..	0	+	.....
6	Fitz-Hugh, T., Jr.: Am. J. M. Sc. **181**: 261, 1931; case 1	65 F	25	Face, lips and nasal mucosa	.....	+	Splenohepatomegaly	58	+	+	Cirrhosis; tonic hepatitis
7	Fitz-Hugh, case 2.....	48 F	Early adulthood	Face, lips and nasal mucosa	.....	+	Splenohepatomegaly	46	0	+	.....
8	Fitz-Hugh, case 3.....	40 F	21	Face, lips, tongue and fingers	.....	+	Splenohepatomegaly	38	0	+	.....
9	Fitz-Hugh, case 4.....	58 F	Adolescence	Face, lips, nasal mucosa and fingers	.....	+	Splenohepatomegaly	37	0	+	.....
10	van Bogaert and Scherer,[2] case 1	73 F	40	Face and hands	.....	+	Familial cirrhosis	..	0	+	.....
11	van Bogaert and Scherer,[2] case 2	46 M	45	Face and fingers	.....	+	Familial cirrhosis	45	+	+	.....
12	Coffin, J., and Bastenie, P.: Bruxelles-méd. **14**: 577, 1934	50 F	..	Face, tongue, lips and nasal mucosa	.....	+	Hepatomegaly	..	..	..	Hemorrhages; fatty degeneration
13	Milbradt, W.: Dermat. Wchnschr. **99**: 973, 1934	47 F	41	Face, tongue, lips and nasal mucosa	.....	+	Cirrhosis	41	+	..	.....
14	Weber [3]	41 M	41	Face, neck, chest and left arm	Dilated capillaries with small round cell infiltration	0	Cirrhosis (syphilitic?)	41	..	..	.....
15	Eller, J. J.: Arch. Dermat. & Syph. **36**: 892, 1937	45 F	41	Cheeks, trunk, legs, arm and oral and nasal mucosa	.....	0	Hepatomegaly (alcoholic cirrhosis?)	44	0	0	.....

REVIEW OF THE LITERATURE

Fifteen cases of cutaneous telangiectasia with associated hepatic disease have been recorded. A summary of these cases is presented in the accompanying table. There were 6 men and 9 women, ranging in age from 35 to 73 years, most of them being in the fifth or sixth decade of life. The cutaneous vascular lesions of the "spider" or a naevus araneus type were observed on the face, neck, nasal mucosa, tongue, lips and hands. In most instances they had appeared during adulthood, and they usually antedated, but often increased rapidly in extent and number with the onset of, the symptoms of the hepatic disorder. In 10 of the cases there was associated familial hemorrhagic telangiectasis. Hepatic cirrhosis was present in 5 cases, metastatic carcinoma of the liver in 2 and hepatosplenomegaly of an undiagnosed type in 6. Jaundice was noted in 2 cases, splenomegaly in 8, syphilis in 1 and pulmonary tuberculosis in 1. Alcohol seemed to be a factor in at least 3 cases. A rare finding in van Bogaert's 2 cases was the presence of both familial cirrhosis and familial telangiectasia.

MATERIAL IN PRESENT STUDY

Six cases of cutaneous angioma of the stellate type associated with hepatic disease have been encountered recently at the Mayo Clinic. The angiomas presented the characteristics previously described. It was noted that when pulsation could not be felt in small lesions, it could be demonstrated by gentle pressure with a diascope. In only 1 instance was there a suggestive familial tendency. The tendency for the cutaneous lesions to antedate the clinical appearance of hepatic disease was apparent. In contrast to the age range of the patients reported on in the literature, 3 of the patients in the present series were adolescent. The hepatic disease was predominantly of the cirrhotic type; in 2 cases this was proved at necropsy. In 2 cases syphilis was present, which, together with the fact that arsenic was probably used therapeutically, may have been an etiologic factor.

REPORT OF CASES

CASE 1.—A college student aged 18 years was seen at the clinic in February 1937. He had been jaundiced for approximately two and a half months. There were no other complaints of consequence. The patient was well nourished and muscular but was slightly pale and moderately jaundiced. Numerous pulsating spider angiomas were observed over the face and over the dorsum of each hand. There was no familial history of such cutaneous lesions. The liver was large and firm; the spleen was also readily palpable. Examination of stained smears of the blood showed moderate hypochromic macrocytic anemia. The value for serum bilirubin varied from 3.2 to 4.5 mg. per hundred cubic centimeters. The value for blood cholesterol was slightly reduced, and the value for plasma protein was lowered (5.8 Gm. per hundred cubic centimeters, with an albumin-globulin ratio

of 1:2). A bromsulphalein test of hepatic function showed grade 3 retention of the dye. The sedimentation rate was considerably increased (117 mm. in one hour). A diagnosis of subacute hepatitis with jaundice and pulsating cutaneous angioma was made.

Case 2.—A girl aged thirteen years was brought to the clinic in September 1936 with the complaint of jaundice and of lesions of the skin. The family history was significant in one respect, in that a sister had a few angiomas on her face. During the first four months of the patient's life she had been definitely jaundiced. This had eventually cleared up, however, and she was well until 1932. At that time angiomas were first noticed on her face, and two years later some appeared on her fingers. Early in 1936 a large number of angiomas appeared on her arms, neck and lips. In April 1936 jaundice again made its appearance, and a month later epistaxis occurred on several occasions. At the time of the patient's last examination she was in excellent general condition except for the fact that she showed the large number of angiomas already referred to and definite jaundice, the liver was large and firm and the spleen extended 2 cm. below the costal margin. Macrocytic anemia was noted. A bromsulphalein test of hepatic function showed grade 3 retention of the dye. The value for serum bilirubin averaged 8 mg. per hundred cubic centimeters. The fragility of the erythrocytes was normal. A flow of bile was obtained on duodenal drainage.

The patient's general condition remained satisfactory until Sept. 17, 1937, when abdominal pain, chills and fever suddenly developed, her temperature rose to 105 F. and she lapsed into coma. Treatment with continuous venoclysis of dextrose was given, and consciousness was regained on the sixth day. Three days later abdominal distention and vomiting developed, followed immediately by gross bleeding from the intestinal tract. The patient died on September 27. Necropsy revealed chronic atrophy of the liver, the organ showing signs of previous extensive necrosis and some areas of nodular regeneration. Free bleeding had occurred into the stomach and intestine. Multiple hemorrhagic ulcers of the ascending colon and edema of the mucosa were also observed; their exact significance could not be determined. The spleen was hypertrophic, weighing 230 Gm.

Case 3.—An unmarried housekeeper aged 35 years registered at the clinic in April 1932. She complained principally of anemia and weakness; splenomegaly had been noted some time previously and she came seeking advice concerning the advisability of splenectomy. On physical examination there were no striking findings except moderate pallor and splenomegaly. Examination of the blood revealed hypochromic anemia, with rather striking leukopenia and a reduction in the number of blood platelets. The value for serum bilirubin was normal, the van den Bergh reaction was indirect and the bromsulphalein test of hepatic function showed grade 3 retention of the dye. On April 2 the spleen, weighing 650 Gm., was removed by Dr. Pemberton. The liver was described as decreased in size and definitely nodular. A specimen for biopsy showed changes rather typical of those of atrophic cirrhosis. There was no ascites, and no extensive collateral circulation had developed. A diagnosis of Banti's disease with portal cirrhosis was made.

The patient has been seen at the clinic at intervals since that time, and the only development of significance has been the appearance of a large number of spider angiomas over the face, trunk and arms. Repeated tests of hepatic function have shown continued improvement.

CASE 4.—A laundryman aged 52 years has been seen at the clinic at various times since 1918. At the time of his first visit he had definite clinical and serologic evidence of tabes dorsalis and was given adequate treatment with arsphenamine and heavy metals. In 1918 jaundice developed during a course of treatment; this persisted for several weeks but gradually cleared. On examination two years later the liver was found to be enlarged and firm. In 1932 ascites developed, and a Talma-Morison omentopexy was performed elsewhere. The liver at that time was described as showing definite evidence of cirrhosis. In April 1937, the patient was again seen at the clinic and was markedly jaundiced. There were multiple large pulsating angiomas of the stellate type scattered over the face, particularly around the eyes (fig. 1), and over the upper part of the trunk. The liver and spleen were both enlarged and readily palpable. Serologic tests for syphilis gave positive reactions; the formed elements of the blood were entirely normal except for a slight increase in the reticulated cells (4.1 per cent) and moderate macrocytosis. Roentgenologic examination for esophageal varices

Fig. 1 (case 4).—Pulsating angiomas involving the eyelids.

gave negative results. A bromsulphalein test of hepatic function showed grade 2 retention of the dye. The blood gave a direct van den Bergh reaction, and the serum bilirubin reading was 5.2 mg. per hundred cubic centimeters. The value for serum protein was normal, but the value for cholesterol was considerably reduced (106 mg. per hundred cubic centimeters). A diagnosis of atrophic cirrhosis on a syphilitic basis was made. Word was received that the patient died in May 1937. The postmortem observations were not available.

CASE 5.—A café operator aged 41 years registered in May 1937 for consideration of his complaint of swelling of the abdomen and legs of three weeks' duration. He had been seen at the clinic in 1925 with a latent syphilitic infection of four years' duration and had been give adequate treatment with the arsenicals and bismuth. A long history of alcoholic excess was noted. Examination revealed scattered stellate angiomas on the face (fig. 2) and trunk of approximately fifteen years' duration. The liver was tremendously enlarged and firm, and the spleen was just palpable (fig. 3). There was considerable ascites, and a collateral circulation was visible. Serologic tests for syphilis gave positive reactions, and the bromsulphalein test of hepatic function showed grade 3 retention of the dye. The value for blood cholesterol was normal. Examination of the formed elements of the blood revealed slight macrocytosis.

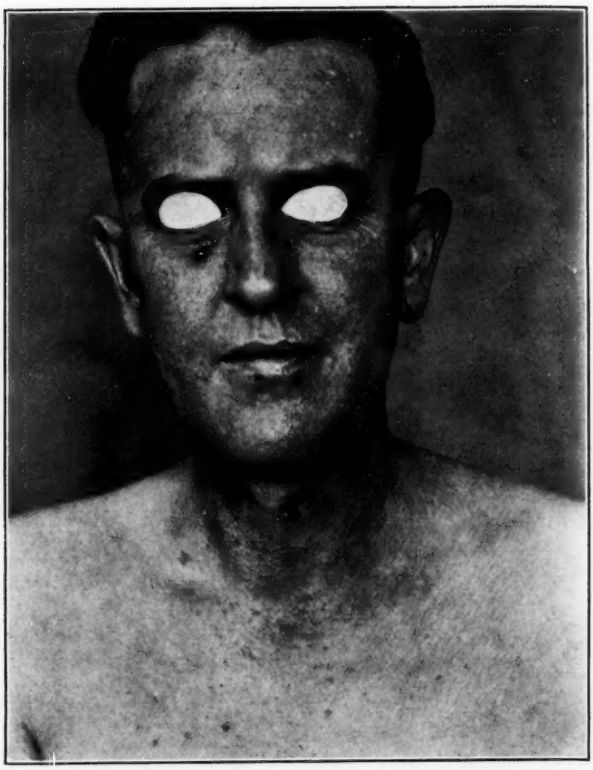

Fig. 2 (case 5).—A large pulsating angioma is seen on the right cheek, and numerous small lesions are scattered on the lips, neck and adjacent upper portion of the chest.

Fig. 3 (case 5).—Ascites and enlargement of the liver and spleen (outlined).

On histologic examination the pulsating lesion on the cheek was found to be an elevated cavernous hemangioma extending from the pars subpapillaris down deep into the cutis. A stroma of loose, young connective tissue surrounded the vascular spaces. On the periphery of the central angiomatous portion of the lesions there was telangiectatic dilatation of the vessels of the subpapillaris.

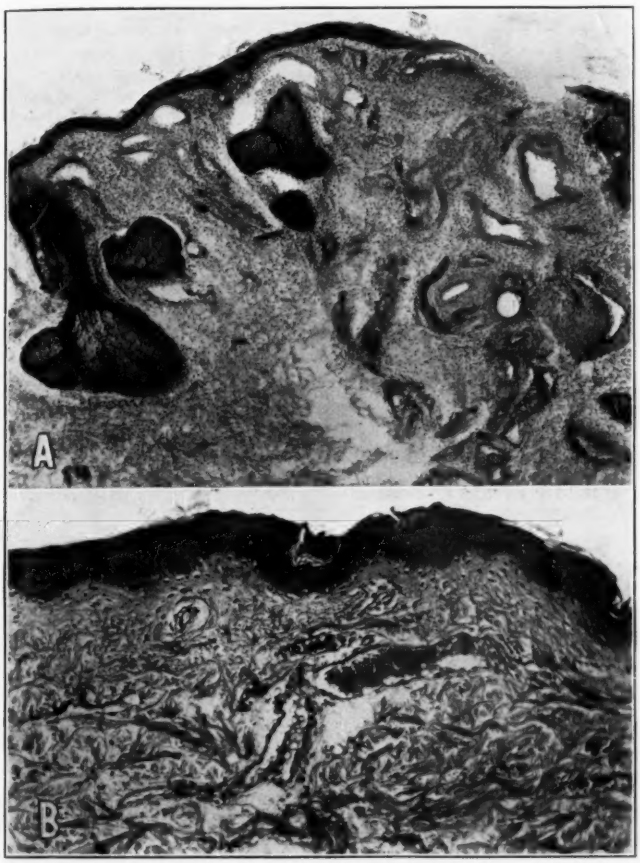

Fig. 4 (case 5).—Sections of the large angioma from the right cheek, showing (*A*) the central angiomatous portion and (*B*) the peripheral telangiectatic dilatation of a blood vessel in the upper portion of the cutis.

Figure 4 shows the central angiomatous element and the peripheral telangiectatic portion of the lesion. A diagnosis of cirrhosis of the liver and pulsating angioma was made, and it was considered that both syphilis and alcohol were factors in the causation of the hepatic disease.

CASE 6.—A girl aged 12 years was admitted to the clinic in September 1937 with the complaint of recurrent nosebleeds and jaundice of one year's duration. Elsewhere the spleen and liver had been found to be enlarged. On examination at the clinic the patient was found to be moderately jaundiced, the liver and spleen were enlarged and there were many stellate pulsating angiomas scattered on the face, neck, arms, hands and right leg. These had been present since the age of 4 years. Laboratory examination revealed values for serum bilirubin which varied from 5.2 to 6.3 mg. per hundred cubic centimeters, a direct van den Bergh reaction being recorded. The values for plasma protein were normal. A galactose tolerance test gave a positive result, raising the suspicion of recent hepatic injury. The cholesterol reading was 116 mg. per hundred cubic centimeters of blood. The formed elements of the blood were not unusual except for a reticulocyte count of 10.6 per cent. During the period of observation the patient had an afternoon temperature of from 99 to 102 F. On October 12 Dr. Walters performed an exploratory operation. The liver was enlarged, and the bile passages showed no signs of past or present obstruction. Cholecystectomy was performed.

One week later the patient became drowsy and semistuporous; blood oozed from around the drainage tube. Death occurred on the eleventh postoperative day, the typical manifestations of hepatic insufficiency being present. Necropsy revealed chronic atrophy of the liver, with marked fibrosis and nodular hyperplasia; the spleen was hypertrophied, weighing 257 Gm. Multiple subpleural and epicardial hemorrhages were also seen, but there was no gross bleeding into the digestive tract, such as occurred in case 1.

COMMENT

The nature of the association of cutaneous angioma and disease of the liver gives rise to much speculation. The established facts concerning it are few. The terms telangiectasis and angioma, applied by different authors to the same cutaneous lesion, imply the concept of an acquired dilatation of existing blood vessels, on the one hand, and the concept of a neoplastic growth, on the other. As a result of the histopathologic examination of a lesion in case 5, it seems likely that both concepts are true, that the lesions are in effect both angiomatous and telangiectatic and that the former condition is primary and the latter secondary.

The feature of pulsation observed by Parkes Weber is an important characteristic, and it suggests a possible relation of the lesion to the glomus bodies described by Masson.[4] Further work is being carried out relative to this point. It is not difficult to conceive how a lesion causing marked dilatation of this arteriovenous anastomosis might result in a cutaneous lesion with the characteristics of pulsation and radiating telangiectasia. In addition, glomus bodies are most frequent on the hands, and it is here that the angiomas are numerous.

4. Masson, M. P.: Les glomus cutanés de l'homme, Bull. Soc. franç. de dermat. et syph. **42**:1174-1245 (July 7) 1935.

That the lesions under consideration are identical with those of hereditary hemorrhagic telangiectasia is apparent from a review of the literature, and the reason why a hereditary tendency is present in some cases and is not apparent in others is best explained on the basis that this familial characteristic is transmitted as a dominant in some persons and as a recessive in others. The characteristic appears to be dominant in hereditary hemorrhagic telangiectasia, whereas it is probably recessive when there is no definite hereditary or familial tendency.

Why a certain percentage of persons born with the inherent characteristic, either dominant or recessive, of being likely to have cutaneous pulsating angiomas should also be born with a liver in which cirrhosis is likely to develop cannot be explained. Possibly these two inherent characteristics are closely related. That there is some factor directly affecting the two conditions is demonstrated by the definite increase in the number of the angiomas with the onset and progression of clinical evidence of hepatic damage and by the fact that occasionally improvement in the hepatic disease has been reported to have coincided with regression of the angiomas.

It is interesting to note, as recorded by Weber,[5] that hepatic cirrhosis may be familial (dominant characteristic). He explained the vascular lesions on the basis of "a congenital-developmental dysplasia of the small blood-vessels, potentially present at birth, though often not manifesting itself by obvious changes till after puberty." He continued as follows: "What is the relationship of the hepatic cirrhosis, when present? Is it the result of an associated developmental dysbiotrophy of the liver—i. e., a congenital tissue or organ inferiorily . . . ?"

Hanes,[6] and later Gjessing,[7] drew attention to the absence of muscular and elastic tissue elements in the vessel walls in cases of hereditary telangiectasia. Memmesheimer [8] noted that the connective tissue in the vicinity of the dilated vessels consisted of a proliferation of young, not well differentiated connective tissue elements. These workers claimed that this inherent weakness in the walls of the vessels and in the supporting connective tissue is a predisposing factor in the development of the vascular lesions. What is the exciting factor which seems so

5. Weber, F. P.: Inborn and Familial Tendency to the Development of Hepatic Cirrhosis, Lancet **1**:305-307 (Feb. 8) 1936.

6. Hanes, F. M.: Multiple Hereditary Telangiectases Causing Hemorrhage (Hereditary Hemorrhagic Telangiectasia), Bull. Johns Hopkins Hosp. **20**:63-73 (March) 1909.

7. Gjessing, E.: Telangiectasia hereditaria haemorrhagica (Osler), Dermat. Ztschr. **23**:193-211, 1916.

8. Memmesheimer, A. M.: Zur Pathogenese der sogenannten essentiellen Telangiektasien, Dermat. Ztschr. **53**:399-413 (April) 1928.

closely related to the liver? The absence of evidence of a toxic or of an infective factor is seen from microscopic examination of the cutaneous lesion, which is, instead, of a neoplastic nature.

From this rather abstruse consideration of a probably not infrequent association come a few practical considerations: Since as a rule the cutaneous manifestations of this syndrome appear before the hepatic manifestations, whenever the former are encountered they should prompt a thorough examination of the liver and its functions; further, a person who exhibits such lesions should be looked on as a possible candidate for hepatic disease, and the use of hepatotoxic drugs such as arsenic and alcohol should be interdicted. A corollary to the foregoing is that in chronic hepatic disease pulsating cutaneous angioma will probably be encountered more frequently if one is watching for it. It appears that the association is not uncommon.

SUMMARY AND CONCLUSIONS

The association of cutaneous pulsating angioma (generalized telangiectasia) and hepatic disease is not uncommon. This association probably depends on two inherent developmental characteristics which are closely related.

The cutaneous lesions are primarily angiomatous in nature and have a border of radiating telangiectatic vessels. These lesions, the development of which represents a recessive characteristic, are identical with those of hereditary hemorrhagic telangiectasia, in which condition their development represents a dominant characteristic.

The hepatic disease is usually chronic, with cirrhosis and atrophy of the hepatic parenchyma predominating. Alcohol, arsenic and syphilis are associated factors.

Progress in Internal Medicine

REVIEW OF NEUROPSYCHIATRY FOR 1938

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The notable events of the year in neuropsychiatry are not as much related to the scientific aspects as to the editorial aspects of the field. Four new journals have appeared in America, and there are reports that two more may be launched! *Psychiatry*, a "journal of the biology and the pathology of interpersonal relations," is published in Washington as a memorial to William A. White. As its name implies, it is concerned largely with the dynamics of psychology in a broad way. *Epilepsia* has been reborn, after a lapse of almost twenty-five years, under the guidance of William G. Lennox in this country. The *Journal of Neurophysiology*, edited by Dusser de Barenne, Fulton and Gerard, fills a long felt need. *Confinia Neurologica* was started by Spiegel and his colleagues in Philadelphia to report advances in "borderland neurology," i. e., the relation of surgery, otology, laryngology, ophthalmology, syphilology and endocrinology to the nervous system. Only one year older is the pioneer of the west coast, the *Bulletin of the Los Angeles Neurological Society*. All this indicates a great increase in neurologic and psychiatric research and a need for publication facilities by an ever increasing number of investigators.

CEREBRAL CIRCULATION

During the past fifteen years there has been a great deal of research work on the circulation of the brain. This was stimulated by the clinical observations and speculations of a century or more, for physicians have long been explaining many symptoms—headaches, fits, transient hemiplegia and aphasia, syncope and hypertension—on the basis of temporary cerebral anemia. At a meeting of the Association for Research in Nervous and Mental Disease in New York in December 1937 a symposium was held on the circulation of the brain and spinal cord. This is reported at length in the proceedings of the society published in 1938, entitled "Circulation of the Brain and Spinal Cord," which will be referred to frequently in this review.

The anatomy of the blood supply to the human brain is unlike that of any other organ. The main arterial supply, coming through the vertebral and the internal carotid arteries, enters the circle of Willis

and thus is distributed to all six cerebral trunks. The sharp bend of the internal carotid artery about the body of the sphenoid bone serves to moderate slightly the more violent fluctuations of pressure, such as may occur in aortic disease with hypertension. The circle of Willis is a protective mechanism of great importance, insuring cerebral blood supply to both hemispheres even if one carotid artery is occluded; moreover, there are anastomoses between the branches of the posterior, middle and anterior cerebral arteries and even between the cerebral branches of the two hemispheres.[1] There are also anastomoses with the external carotid artery, usually by way of the ophthalmic artery.

Histologically, cerebral vessels differ from vessels elsewhere in the body mainly because their inner elastic membrane is thicker than that of the other arteries and as age advances it hypertrophies and divides into two or more laminas. This strengthening of the inner layer of the arterial wall is probably important in the brain because of the weakness of the outer layers. The adventitia is merely a loose network filled with fluid, being limited outwardly by a layer of glia; thus the perivascular space of Virchow and Robin is formed. Around small vessels it is not a clearly defined space; it is more potential than actual, unless distended with fluid. As the vessels become larger and approach the meninges, the space is more distinct, at last becoming continuous with the arachnoid space. These perivascular spaces are analogous to the lymphatic ducts of other organs.

The first quantitative studies of the cerebral blood supply were made by Craigie [2] and have been confirmed by recent workers. White matter has about 200 to 300 mm. of capillary length per cubic centimeter of brain substance, while gray matter has from 600 to 1,000 mm. The difference in blood supply is further magnified by the fact that the capillaries are of larger caliber in the white matter; so even less blood is exposed to the capillary wall—for the smaller the capillary, the greater the amount of blood that comes in contact with the wall of the vessel and the greater the metabolic exchange between blood stream and tissue. Finley's [3] excellent preparations show the relative difference in the capillary supply of nuclei, cortex and white matter so conspicuously that one does not need quantitative estimates to be convinced. The most vascular parts of the gray matter are the paraventricular and supraoptic nuclei, but even these have only about one-fifth as rich a capillary bed as has

1. Fay, T.: Cerebral Vasculature: Preliminary Report of Study by Means of Roentgen Ray, J. A. M. A. **84**:1727 (June 6) 1925.

2. Craigie, E. H.: J. Comp. Neurol. **31**:429, 1920; A. Research Nerv. & Ment. Dis., Proc. **18**:3, 1938.

3. Finley, K.: A. Research Nerv. & Ment. Dis., Proc. **18**:94, 1938.

skeletal muscle.[4] Wolff [5] has shown that capillary density is correlated not merely with the number of nerve cells in a given region but with the surface area of these nerve cells; nerve cells with few dendrites have less capillary network around them than nerve cells with many dendrites. This anatomic observation corroborates Gerard's [6] general thesis that the number of capillaries in a given region is roughly proportional to the oxygen consumption.

CEREBRAL THROMBOSIS

There have been much discussion and much misunderstanding concerning the question of end arteries in the brain. Cohnheim,[7] the originator of the end artery theory, has been repeatedly quoted and often misunderstood. Part of the confusion has arisen from the fact that different laboratory animals have been used and comparisons have been made with man. Wislocki [8] has shown that in the opossum there are simple and complete end arteries, even down to the capillary loops. The vascular architecture in cats, rabbits and monkeys more closely approximates that found in human brains. Campbell [9] gives the most accurate observations available at present. He shows that in the cat, anastomoses do occur between larger arteries. They are found most frequently near the periphery of the arterial trees, especially between branches in the pia. Here the connecting arteries are from 70 to 90 microns in diameter. These arteries are important since they are the ones that directly supply the cortical gray matter. Few of the penetrating arteries anastomose with each other until they reach precapillary size. In the striatum and white matter, anastomosis between arteries is less common.

Cohnheim apparently knew that there are capillary anastomosis in the brain and some connection between the pial vessels, but he underestimated the amount and stated that if such connections do occur they are of no functional importance. Recent animal experiments show that anastomoses between arteries are common and are of importance in saving the brain from small infarctions, even though the collateral blood supply is not enough to obviate larger infarcts. Putnam's [10] demonstration of small areas of reaction or necrosis around minute thrombi in the brain emphasizes the importance of these connections between arteries

4. Cobb, S., and Talbott, J. H.: Tr. A. Am. Physicians **42**:255, 1927.

5. Wolff, H. G., and Dunning, H. S.: J. Comp. Neurol. **67**:433, 1937.

6. Gerard, R. W.: A. Research Nerv. & Ment. Dis., Proc. **18**:316, 1938.

7. Cohnheim, J.: Untersuchungen über die embolischen Processe, Berlin, A. Hirschwald, 1872.

8. Wislocki, G., and Campbell, A. C. P.: Anat. Rec. **67**:177, 1937.

9. Campbell, A. C. P.: A. Research Nerv. & Ment. Dis., Proc. **18**:69, 1938.

10. Putnam, T. J., and Alexander, L.: A. Research Nerv. & Ment. Dis., Proc. **18**:544, 1938.

and between veins. Alexander and Putnam [11] point out that the vulnerability of the brain to lack of oxygen and its lack of ability to repair damage are the important things to consider. The peculiarities of the blood supply must be taken into account, but are important only when related to the special reactions of the cerebral tissues. Thus focal anemia is one of the important causes of cerebral lesions.

The mechanism of gross infarction is fairly well understood. While the question of the effect of arterial spasm remains unsolved, the effects of small vascular obstructions are definitely recognizable; such lesions probably cause a number of "diseases," many of them having heretofore been considered "idiopathic" or mysterious. Hemorrhagic necrosis, encephalomalacia, some kinds of encephalopathy and some types of perivascular hemorrhage are probably varying degrees of red and white infarction. Evans [12] thinks the varying degree and the varying suddenness of oxygen deprivation are more important: A red infarct is formed when the circulation is merely slowed; sudden complete occlusion leads to white necrosis and cyst formation. All infarcts at first show some diapedesis of red blood cells and only later grow truly white.

APOPLEXY

Numerous theories have been advanced to explain cerebral hemorrhage. The simplest and oldest is that the vessel wall is weakened by senile changes or disease and that the blood pressure inside the artery ruptures the pathologic wall. Charcot [13] believed that "miliary aneurysms" are common and that their rupture causes many hemorrhages. Böhne,[14] Globus [15] and others have supported the thesis that gross cerebral hemorrhage takes place only from vessels that lie in softened brain substance. This theory seems to me not only unproved but unreasonable. If, as Globus described it, partial softening of brain substance does take place about arteries, the fluid and soft substance would surround the vessel at a pressure practically as great as that of the normal tissue, i. e., 150 mm. of water, whereas the pressure within the artery would be about 1,500 mm. of water. It is apparent that what keeps the blood from bursting out is not the support of the surrounding brain tissue or fluid but the elastic and muscular coats of the arterial wall. These coats, as has already been mentioned, have a somewhat different arrangement in cerebral arteries from that in arteries elsewhere in the body. The

11. Alexander, L., and Putnam, T. J.: A. Research Nerv. & Ment. Dis., Proc. **18**:471, 1938.

12. Evans, J. P., and McEachern, D.: A. Research Nerv. & Ment. Dis., Proc. **18**:379, 1938.

13. Charcot, J. M., and Bouchard, C.: Arch. de physiol. norm. et path. **1**: 110, 643 and 725, 1868.

14. Böhne, C.: Beitr. z. path. Anat. u. z. allg. Path. **78**:270, 1927.

15. Globus, J. H.: A. Research Nerv. & Ment. Dis., Proc. **18**:438, 1938.

strength of the wall is particularly dependent on the inner elastic lamina, and as age advances this lamina hypertrophies and splits up.[16] Degenerative processes often weaken this wall, and hemorrhage is the simple result of bursting. Of course an aneurysmal dilatation may form before the rupture, but I doubt if congenital aneurysm without degenerative disease is a common cause of cerebral hemorrhage.

Merritt and Aring[17] discuss the differential diagnosis of cerebral hemorrhage and thrombosis. They believe that it is of more than academic significance, because the immediate prognosis for life and the ultimate prognosis for return of function are different in these cases. Also the possibility of surgical intervention and removal of the clot, which has been suggested by several neurosurgeons,[18] enhances the significance of the diagnosis. Factors which have significance in regard to the differential diagnosis and which point to the diagnosis of cerebral hemorrhage are:

1. Onset with headache and vomiting
2. Onset with convulsions—especially if syphilis can be excluded
3. Stiffness of the neck and Kernig's sign
4. Dilatation of the pupil on the side opposite the lesion, or bilateral absence of the light reflex
5. Conjugate deviation of the head and eyes
6. A bilateral Babinski reflex
7. Progression of the focal symptoms over a period of twelve to fourteen hours
8. Leukocytosis, with counts of over 12,000 per cubic millimeter
9. A cerebrospinal fluid pressure greater than 350 or 400 mm., regardless of whether the fluid is bloody or not
10. A bloody cerebrospinal fluid with a xanthochromic supernatant fluid
11. A clear or slightly yellow cerebrospinal fluid with pleocytosis (more than 100 cells per cubic millimeter), when syphilis and septic embolus can be excluded

A false statement often found in the literature and more often quoted is that the signs and symptoms of cerebral thrombosis frequently develop slowly. The slow development of focal symptoms (hemiplegia, aphasia

16. Hackel, W. M.: Virchows Arch. f. path. Anat. **266**:630, 1928.

17. Merritt, H. H., and Aring, C. D.: A. Research Nerv. & Ment. Dis., Proc. **18**:682, 1938.

18. Bagley, C., Jr.: Spontaneous Cerebral Hemorrhage: Discussion of Four Types, with Surgical Considerations, Arch. Neurol. & Psychiat. **27**:1133 (May) 1932. Penfield, W.: Canad. M. A. J. **28**:369, 1933. Craig, W. M., and Adson, A. W.: Spontaneous Intercerebral Hemorrhage: Etiology and Surgical Treatment, with Report of Nine Cases, Arch. Neurol. & Psychiat. **35**:701 (April) 1936.

and hemianopia) occurs so rarely, if at all, in cases of cerebral vascular lesions that such a diagnosis is extremely hazardous.[19] This is especially true for patients with a normal blood pressure and normally functioning kidneys. In such cases an examination of the cerebrospinal fluid is of great importance, since an expanding lesion may cause an increase in the cerebrospinal fluid pressure which can be detected before the development of choked disks.

For patients with cerebral vascular accidents who die and are studied post mortem the clinical diagnosis usually is "hemorrhage," but at least half of them show "softening," i. e., thrombosis with infarction. The clinical studies of Merritt and Aring show that probably only one fifth of the vascular accidents in which death does not occur can be attributed to hemorrhage, the remaining 80 per cent being due to thrombosis and rarely embolus.

Experiments by Schmidt,[20] Pool,[21] Thomas [22] and others have shown that carbon dioxide, glyceryl trinitrate, acetylcholine, ether and alcohol are the best cerebral vasodilators. It seems to me that they should be used therapeutically early in cases of cerebral thrombosis, because restoration of circulation to an infarcted area within a few hours of the onset will probably save a great deal of function that will be permanently lost if the orthodox treatment of rest and morphine is followed. In fact, I consider morphine as probably harmful in such cases. I would rather have the patient kept awake, with his blood pressure up and his head moderately raised. Caffeine in large doses may cause vasoconstriction; so it should be used with caution if at all.

REGULATION OF THE CEREBRAL BLOOD SUPPLY

In the vertebrate organism there are two main integrating systems—the blood stream and the nerves. These two reach every part of every living organ. Between these two principal integrators there is a reciprocal relation that is of great importance. The brain, like every other organ, is dependent on its blood supply; but the blood supply is dependent on a normally functioning brain, for blood flow to the various organs, even to the brain itself, is largely regulated by the vasomotor centers of the brain and spinal cord (see the accompanying diagram). The central nervous system contains the head ganglions of the autonomic nervous

19. Merritt, H. H., in Blumer, G.: The Practitioners Library of Medicine and Surgery, New York, D. Appleton-Century Company, Inc., 1936, vol. 9, chap. 23.

20. Schmidt, C. F., and Hendrix, J. P.: A. Research Nerv. & Ment. Dis., Proc. **18**:229, 1938.

21. Pool, J. L.; Nason, G. I., and Forbes, H. S.: Cerebral Circulation: Effect of Nerve Stimulation and Various Drugs on the Vessels of the Dura Mater, Arch. Neurol. & Psychiat. **32**:1202 (Dec.) 1934.

22. Thomas, C. B.: Cerebral Circulation: Effect of Alcohol on the Cerebral Vessels, Arch. Neurol. & Psychiat. **38**:321 (Aug.) 1937.

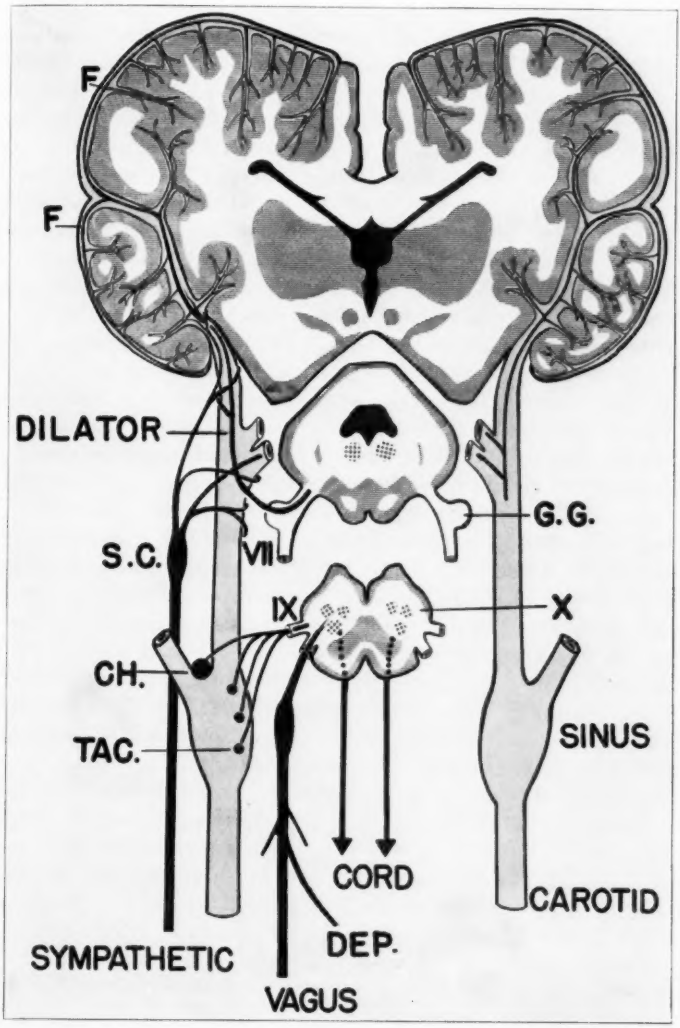

Diagram of the physiologic mechanisms concerned in maintaining the blood flow to the brain.

system, which in turn control the vegetative nerves to the heart and vessels. Thus a lesion in the heart and a lesion in the hindbrain are equally lethal.

The extracerebral control of cerebral circulation has been worked out carefully by Heymans [23] and his co-workers [24] in a series of classic experiments. Weiss [25] summarizes this work and describes his own contributions to the subject. He says that the circulation of the brain acts like that of an organ with continuous maximal activity; it must be served, even at the expense of other organs. To maintain this all-important blood supply at a relatively constant rate there are several physiologic mechanisms. These are indicated in the accompanying diagram.

The principal regulator of the amount of blood that flows to the brain is the blood pressure in the carotid and vertebral arteries. In man the vertebral arteries are relatively small, and the carotid arteries control most of the circulation to the cerebrum; so the carotid sinus mechanism is most important. In the wall of this sinus at the bifurcation of the external and internal carotid arteries lies a structure with sinusoidal apertures that are bathed in the blood that enters the sinus. Nerve endings in this structure (*CH.* in the figure) are sensitive to changes in carbon dioxide tension: If the content is high, impulses from this chemical end organ pass along the carotid sinus nerve to the hypoglossal root (*IX* in the figure) in the medulla oblongata, and there reflexly increase the blood pressure via the vasomotor center and the pathways to the spinal cord. Small tactile (*Tac.*) organs that lie in the wall of the carotid sinus respond to stretching or contraction of the wall: If the wall is stretched, impulses go to one of the medullary centers of the vagus nerve (*X*) and thence reflexly lower the blood pressure via both the vagus nerve and the vasodilator mechanism of the spinal cord. Contraction of the wall of the sinus has the opposite effect. Similar organs that register stretch are found in other vessels, for example, the aorta. Impulses from this source travel along the aortic depressor nerve (*DEP.*) and reflexly lower the blood pressure. The vagus nerve itself contains both afferent and efferent fibers of the heart and other viscera; so vagovagal reflexes can also control the blood pressure. Such, briefly, is the extracerebral control of the blood supply to the brain.

Within the skull there is an intrinsic or cerebral control. Penfield [26] and Forbes [27] have shown that the cerebral vessels have both a vaso-

23. Heymans, C.: Bruxelles-méd. **16**:1411, 1936.

24. Bouchaert, J. J., and Jordan, F.: Rev. belge sc. méd. **9**:12, 1937.

25. Weiss, S.: A. Research Nerv. & Ment. Dis., Proc. **18**:571, 1938.

26. Chorobski, J., and Penfield, W.: Cerebral Vasodilator Nerves and Their Pathway from the Medulla Oblongata, with Observations on the Pial and the Intracerebral Plexus, Arch. Neurol. & Psychiat. **28**:1257 (Dec.) 1932.

27. Forbes, H. S., and Cobb, S.: A. Research Nerv. & Ment. Dis., Proc. **18**: 201, 1938.

constrictor and a vasodilator innervation. The fine fibers (*F.*) that follow the smaller vessels seem to have a vasomotor function. By physiologic experiments on cats, rabbits and monkeys, vasoconstrictor nerves have been proved to be present on vessels of the parietal cortex [27] and basal ganglions.[28] The constriction of arteries which follows stimulation of these nerves is only about one-tenth as great as the constriction of arteries of a similar size in the skin and other extracranial organs. The vasoconstrictor innervation reaches the brain by way of the cervical sympathetic nerves and the superior cervical ganglion (*S.C.*).

I do not believe with Ricker [29] that the nervous control of the vessels plays much of a role in the causation of cerebral lesions. There is fairly good clinical evidence that cerebral vessels may contract in a spasmodic way and cause temporary symptoms, but Forbes [27] has shown that the control is slight under normal conditions. In scars and sclerotic areas the vasomotor nerves may have a lowered threshold which predisposes the vessels to spasmodic constriction and anoxia of the tissue.

Vasodilator nerves have also been found on cerebral vessels of the parietal cortex. Stimulation experiments [27] have shown that these fibers leave the hindbrain with the facial nerve and pass to the geniculate ganglion (*G.G.*) along the great superficial petrosal nerve and thence to the carotid artery and its branches.

Fog [30] and Forbes [31] independently demonstrated that if the systemic blood pressure of an animal is made to fall, from whatever cause, to a low level, the arteries of the pia will dilate rapidly and widely. In the cat the critical level of systolic blood pressure at which this usually occurs is about 60 mm. of mercury. The immediate cause of arterial dilatation seems to be the sudden slowing of the blood flow which obviously follows the drop in pressure and can be seen in the living vessels under the microscope. The importance of this phenomenon cannot yet be estimated, but it must partly compensate for the decreased cerebral blood flow of a failing circulation. Moreover, it may occur in other organs, although it has been observed only in the brain.

With so many regulatory mechanisms one might expect frequent changes in the caliber of the vessels and in the blood flow, but the flow is remarkable for its steadiness.[32] The constant temperature of the

28. Schmidt, C. F.: Am. J. Physiol. **110**:137, 1934.

29. Ricker, G.: Sklerose und Hypertonie der innervierten Arterien, Berlin, Julius Springer, 1927, p. 193.

30. Fog, M.: Cerebral Circulation: Reaction of the Pial Arteries to a Fall in Blood Pressure, Arch. Neurol. & Psychiat. **37**:351 (Feb.) 1937.

31. Forbes, H. S.; Nason, G. I., and Wortman, R. C.: Cerebral Circulation: Vasodilation in the Pia Following Stimulation of the Vagus, Aortic and Carotid Sinus Nerves, Arch. Neurol. & Psychiat. **37**:334 (Feb.) 1937.

32. Lennox, W. G.: Constancy of the Cerebral Blood Flow, Arch. Neurol. & Psychiat. **36**:375 (Aug.) 1936.

brain, the "closed box" arrangement, the mixture of blood by anastomosis, the governing action of carbon dioxide, the moderating reflexes from vagodepressor nerves and the carotid sinus, and the paucity of direct vasomotor control, all tend to make the cerebral blood flow constant. The fact that it does not fluctuate much under physiologic conditions may be explained teleologically by assuming that delicate nerve tissue requires a steady supply of oxygen rather than a rich one. This supposition is reasonable because there is evidence that a rapid change in the environment of nerve cells is more harmful than a slow but more extensive change. Probably a constant supply of oxygen to the brain is more important than an exceptionally rich one; so the brain as a whole has a steady blood flow. The lower centers in the brain stem, being active throughout life at all times, need an even, continuous flow, for on them vital functions depend. The cerebral hemispheres, however, being more specialized and less continuously active, have a less steady blood flow, and those parts of the cerebral cortex most actively functioning at any given time have temporary and local changes in blood flow.[6]

Lennox, Gibbs and Gibbs [33] succinctly state the important point about the regulation of circulation in the brain when they say that gross changes in total cerebral flow probably are not adjustments to nutritional requirements of the brain cells but are directed toward the maintenance of a constant tension of carbon dioxide and a constant hydrogen ion concentration in the nerve cells. Changes in blood flow as a result of alterations in metabolic activity are probably local. According to these authors, the unique characteristic of the cerebral blood flow as compared to the blood flow in other organs is that it is steady, showing little variation.

SYNCOPE, CONVULSIONS AND MIGRAINE

Syncope from various causes is discussed by Lennox, Gibbs and Gibbs [33] as well as by Weiss.[25] In most cases it is due to some fundamental circulatory change—cardiac inhibition, failure of the heart or vasodilatation; each may cause ischemia of the brain and fainting. The group of cases in which no failure of circulation is observable might be explained by vasoconstriction in the brain, but the evidence is against this explanation. In the first place, the loss of consciousness comes on too suddenly to be readily explained by such a mechanism, and, secondly, no change in total cerebral blood flow is observable. Since I do not believe that consciousness is controlled by centers which can be switched on and off by reflex neural discharges, the remaining possibility seems to be that stimuli from local areas of ischemia from stimulation of end organs in the carotid sinus, heart and great vessels may induce discharges of neurons in the cerebral cortex which spread like the epileptic dis-

33. Lennox, W. G.; Gibbs, F. A., and Gibbs, E. L.: A. Research Nerv. & Ment. Dis., Proc. **18**:277, 1938.

charge and blot out consciousness in a few seconds. The similarity of this syndrome, as described by Weiss, to an epileptic fit may be striking.

Another set of causes of unconsciousness is discussed by Lennox, Gibbs and Gibbs,[33] who wisely avoid definition of the term and speak generally of "cerebral activity" and its cessation. They point out that the patient ceases to respond to stimuli when the oxygen content of the blood falls to a point between 30 and 24 per cent of saturation. Sugar is the other constituent of the blood about which data are available. When there is less than 30 mg. of sugar per hundred cubic centimeters of blood, coma and convulsions may supervene.

Many convulsions are caused by asphyxia and vascular disorders, but recent work shows that epileptic seizures are not often caused by widespread vascular changes within the brain. There are many clinical observations that show that ischemia causes discharge in the central nervous system (fits). Seizures due to heart block, cerebral infarct, strangulation, cyanide, metrazol and insulin poisoning and certain other factors closely resemble the fits that are ascribed to "cerebral vascular spasm." Oxygen deficiency in the cells of the brain is doubtless one of the commonest causes of convulsions. But that does not mean that widespread spasm of the arteries is present. On the other hand, local vasospasm cannot now be disregarded as one cause of epileptiform seizures, and the proof that there is vasomotor innervation of the cerebral vessels makes such a mechanism one of the probable causes of certain types of seizures.

Penfield [34] finds at operation many abnormalities of the cerebral circulation, but none that appears to be causative of the seizures. The fit seems to leave behind it a more or less local area of overstimulated brain which, because of its overactivity, shows local dilatation of vessels and a rapid blood flow. The commonest phenomenon observed is the cessation of visible pulsation in the cerebral arteries during a seizure.

The headaches supposed to be due to vascular disturbances in the brain, both typically migrainous and miscellaneous, are explained by Wolff and Graham on the basis of changes in pulse pressure in the extracerebral vessels. Experiments on patients with ergotamine tartrate and histamine have led to a great advance in the treatment of migraine, a common and incapacitating disease. The report by Graham and Wolff [35] on their investigations and on the work of others is one of the most encouraging contributions to the symposium. An accurate knowledge of the action of ergotamine is of prime importance to the study of migraine, and the difference in physiologic effect reported by the different experi-

34. Penfield, W.: A. Research Nerv. & Ment. Dis., Proc. **18**:605, 1938.

35. Graham, J., and Wolff, H. G.: A. Research Nerv. & Ment. Dis., Proc. **18**:638, 1938.

menters [36] should be the subject of further study. The cause of headache, however, is far from settled: Penfield [37] and McNaughton [38] describe sensory fibers from the trigeminal nerve to the dural sinuses; they have observed pain similar to migraine caused by traction on the veins that enter the sinuses.

ALCOHOLISM

Five years ago it was almost universally believed that the lesions and symptoms caused by chronic alcoholism were due to the toxic effect of alcohol itself. The pioneer papers of Shattuck [39] and Meyer [40] were scarcely known. Now there is excellent proof [41] that "alcoholic neuritis" is caused by lack of vitamin B_1, and there is good evidence that "Korsakoff's psychosis" and "alcoholic hallucinosis" are merely clinical variants of pellagra.[42] Thus the treatment of these syndromes has changed from a vague "supportive" regimen to specific therapy with large amounts of vitamin: 20 to 40 mg. of crystalline vitamin B_1 (or its equivalent) for alcoholic neuritis and for hallucinosis, memory defect, glossitis and erythema. Recently vitamin C has also been found to be deficient in patients with chronic alcoholism. Plaut [43] reported a low content in the blood and spinal fluid of a few patients, and Alexander and his associates [44] have studied 106 alcoholic addicts. The evidence is definite that vitamin C is at an abnormally low level (averaging about half the normal value); but whether or not this deficiency is important or incidental is not yet known, although scurvy is not uncommon in alcoholic addicts. The propensity of these persons to have subdural hematomas may be due to the scorbutic friability of the blood vessels.[45] It has been suggested that the hemorrhagic lesions of the midbrain in cases of Wernicke's "polioencephalitis" might be due to scurvy, but

36. Pool, L. J., and Nason, G. I.: Cerebral Circulation: Comparative Effect of Ergotamine Tartrate on the Arteries in the Pia, Dura and Skin of Cats, Arch. Neurol. & Psychiat. **33**:276 (Feb.) 1935. Schmidt and Hendrix.[20]

37. Penfield, W.: Proc. Am. Neurol. A., 1938, to be published.

38. McNaughton, F. L.: A. Research Nerv. & Ment. Dis., Proc. **18**:178, 1938.

39. Shattuck, G. C.: Am. J. Trop. Med. **8**:539, 1928.

40. Meyer, A.: Schweiz. med. Wchnschr. **2**:1243, 1932.

41. Romano, J.: Am. J. M. Sc. **194**:45, 1937. Goodhart, R., and Jolliffe, N.: Effects of Vitamin B (B_1) Therapy on the Polyneuritis of Alcohol Addicts, J. A. M. A. **110**:414 (Feb. 5) 1938.

42. Spies, T. D., and Cooper, C.: Internat. Clin. **4**:1, 1937.

43. Plaut, F., and Bülow, M.: Ztschr. f. d. ges. Neurol. u. Psychiat. **152**: 84, 1935.

44. Alexander, L.; Pijoan, M.; Schube, P. G., and Moore, M.: Cevitamic Acid Content of Blood Plasma in Alcoholic Psychoses, Arch. Neurol. & Psychiat. **40**:58 (July) 1938.

45. Ingalls, T. H.: New England J. Med. **215**:1279, 1936.

recent experiments of Alexander, Pijoan and Myerson [46] have shown that these lesions are due to lack of vitamin B_1.

The treatment of delirium tremens also has been improved greatly. In the past it has often been stated that the use of alcohol should be continued, for the delirium is due to the sudden cessation of drinking. These beliefs, which never had a sound clinical basis, have now been thoroughly controverted by Piker,[47] who found that in 205 of 275 patients with delirium tremens, delirium developed while they were still drinking. The theory that the patient should be dehydrated because he may have cerebral edema ("a wet brain") has also been satisfactorily thrown into the discard. Nicholson and Taylor [48] have shown that alcohol causes diuresis with retention of potassium which rapidly dehydrates the body and may cause most of the symptoms of the alcoholic "hangover." It is well known that water is greatly craved some hours after a debauch. It has also been demonstrated by Thomas, Semrad and Schwab [49] that the amount of total protein in the serum is greatly reduced in patients with delirium tremens. These authors have demonstrated the fact that patients with delirium tremens improve more rapidly if the intake of fluid is drastically increased. A liter of physiologic solution of sodium chloride should be given parenterally as soon as possible, and saline solution and other fluids should be given by mouth until at least 3,000 cc. is ingested per day. All vitamins should be given in large amounts, especially B_1. Paraldehyde is the best sedative. With such a regimen the delirium can be shortened and lives can be saved. Lumbar puncture is useful in respect to the diagnosis, to indicate whether or not there is evidence of injury to the brain, but it is not important therapeutically.

SCHIZOPHRENIA

In the review of neuropsychiatry for 1937 I [51] discussed at length the status of the insulin treatment of schizophrenia. Since then the treatment has been applied to hundreds of patients in various state and private hospitals. The initial enthusiasm is beginning to wane. Critical judgment of the results indicate that treatment with insulin and with metrazol certainly has value and often brings about a remarkable remis-

46. Alexander, L.; Pijoan, M., and Myerson, A.: Tr. Am. Neurol. A., 1938, to be published.

47. Piker, D.: Am. J. Psychiat. **93**:1387, 1937.

48. Nicholson, W. M., and Taylor, H. M.: J. Clin. Investigation **17**:279, 1938.

49. Thomas, J.; Semrad, E. V., and Schwab, S. M.: Am. J. M. Sc. **195**: 820, 1938.

50. Footnote deleted by the author.

51. Cobb, S.: Review of Neuropsychiatry for 1937, Arch. Int. Med. **60**: 1098 (Dec.) 1937.

sion of symptoms; nevertheless many patients have a relapse, and many would have had remissions anyway. The data are well summarized by Paskind,[52] Malzberg[53] and Ross.[54] The general consensus appears to be that both procedures constitute a distinct contribution to the treatment of schizophrenia, though few workers now report the astonishingly high rates of remission which were claimed in some of the earlier papers. Reports are also appearing which suggest that metrazol may be of value for patients with depressive reactions.[55] The value of the proper psychotherapeutic management of the patient, particularly during treatment with insulin, is still stressed. An interesting technical development consists of the recognition of the therapeutic value of prolonged coma, i. e., reactions varying between coma and twilight states and lasting over several days.

The death rate associated with both forms of therapy remains low, the most prevalent causes associated with insulin therapy being cardiac collapse and pulmonary edema. With metrazol therapy, pulmonary complications, particularly aspiration pneumonia, are the most frequent causes of death. A great deal of investigative work has been reported. From a number of sources it appears that the major effects of both types of therapy are on the oxygen consumption of the central nervous system and on the autonomic nervous system. Attempts to duplicate the therapeutic results by exposure to low oxygen tensions have been unsuccessful, and attention at present is turned to the autonomic nervous system as the key to the therapeutic mechanisms.

A trend in this treatment that gives pause to the careful physician is the use of other convulsant drugs, either alone or combined with insulin, when insulin alone does not work. As I mentioned last year, camphor and metrazol[56] have been used in this way. These mixtures of drugs makes one lose hope that any specific treatment for schizophrenia has been found. Probably some severe general reaction in the brain, like anoxia, is the therapeutic agent.

The question of whether permanent damage to the brain results from the use of either insulin or metrazol has been actively debated during the last year. Many, although not all, animal experiments have shown that extensive damage, usually accompanied by multiple areas of hemorrhage,

52. Paskind, H. A., in Reese, H. H.; Paskind, H. A., and Sevringhaus, E. L.: Yearbook of Neurology, Psychiatry and Endocrinology for 1937, Chicago, The Year Book Publishers, Inc., 1938.

53. Malzberg, B.: Psychiatric Quart. **12**:528, 1938.

54. Ross, J. R.: A Statistical Study of Results in the New York State Hospitals, read before the American Psychiatric Association, San Francisco, June 9, 1938.

55. Low, A. A.; Sonenthal, I. R.; Blaurock, M. D.; Kaplan, M., and Sherman, I.: Metrazol Shock Treatment of "Functional" Psychoses, Arch. Neurol. & Psychiat. **39**:717 (April) 1938.

56. von Meduna, L.: Ztschr. f. d. ges. Neurol. u. Psychiat. **152**:235, 1935.

may occur after both types of therapy; and in a certain number of patients dying from the treatments, comparable lesions have been observed. There is some clinical evidence which suggests that damage of an irreversible nature occurs in the brain, but the fine changes in higher functions seen after damage to the frontal lobe have not yet been found in patients treated with either insulin or metrazol. Nevertheless, it is notoriously difficult to make an estimate of these finer mental functions, especially when the patient was not examined before his illness.

It is particularly alarming to learn, on the good authority of Weil's [57] experiments, that insulin given to animals, in doses comparable to those used for human beings, causes widespread degeneration and necrosis of the ganglion cells of the brain. These well controlled experiments indicate that the damage is caused by the cumulative effect of repeated large doses of insulin.

Other convulsants, such as thujone and camphor, have been shown [58] to cause lesions in the cerebral cortex, consisting of chromatolysis or even necrobiosis of the ganglion cells and petechial hemorrhages. Little work has been done on the effects of metrazol on cerebral ganglion cells, but at the last meeting of the American Neurological Association, Alpers [59] presented data on 7 monkeys which had been given convulsive doses of metrazol. Three brains were normal, and 4 showed cell changes, 3 of these having subarachnoid hemorrhages.

Such evidence makes me believe that the therapeutic effect of insulin and metrazol may be due to the destruction of great numbers of nerve cells in the cerebral cortex. This destruction is irreparable. The therapy may be justifiable in cases of schizophrenia if experience proves that treatment results in permanent improvement, but the physician recommending these radical measures should do so with his eyes open to the fact that he may be removing symptoms by practically destroying the most highly organized part of the brain. The use of these measures in the treatment of psychoses and neuroses from which recovery may occur seems to me entirely unjustifiable.

New light has been thrown on the etiology of psychoses by Elvidge,[60] of the Montreal Neurological Institute. For several years he has been

57. Weil, A.; Liebert, E., and Heilbrunn, G.: Histopathologic Changes in the Brain in Experimental Hyperinsulinism, Arch. Neurol. & Psychiat. **39**:467 (March) 1938.

58. Opper, L.: The Pathology of Thujone and Monobromated Camphor Convulsions Compared with the Pathology of Human Epilepsy, Arch. Neurol. & Psychiat., to be published.

59. Strecker, E. A.; Alpers, B. J.; Flaherty, J. A., and Hughes, J.: Tr. Am. Neurol. A., 1938, to be published.

60. Elvidge, A. R., and Reed, G. E.: Biopsy Studies of Cerebral Pathologic Changes in Schizophrenia and Manic-Depressive Psychosis, Arch. Neurol. & Psychiat. **40**:227 (Aug.) 1938.

carefully studying biopsy specimens from the brains of patients with schizophrenia and manic-depressive psychosis. For years pathologists have searched in vain for significant changes in the brains of patients who die while suffering from these diseases. Now Elvidge and his colleagues have shown that changes do occur in the oligodendroglia and that these can be demonstrated in specimens taken during life and fixed immediately for staining by the Hortega method. The oligodendroglia cells were found to be swollen, with shortened processes, and the nuclei were either normal or pyknotic. All but 1 of 13 patients with typical schizophrenic syndromes showed definite swelling of the oligodendroglia; another showed it on one occasion but not on reexamination a year later. Specimens from the brains of 5 patients with manic-depressive psychoses all showed swelling, although in 1 patient it was slight. The control material used was large, because Elvidge had access to specimens taken at many operations. It is significant that in this material swollen oligodendroglia cells were observed in several specimens from patients operated on for convulsions, and these appeared to be the patients who had stupor or other mental symptoms at the time of operation. This suggests that the histologic changes observed may not be specifically related to schizophrenia or manic-depressive psychosis but to the presence of any abnormal mental state. The observations are important and should be carried out extensively and with many controls. When skilfully performed, there is no reason to suppose that removal of biopsy specimens from the cortex does harm to cerebral function. In fact, I think it a less harmful procedure than the production of one therapeutic convulsion.

SCIATICA

It has long been suspected by clinicians that pain in the sciatic nerve is usually due to mechanical difficulties in the sacrum and lower portion of the spine and that it had little to do with "neuritis." The work of orthopedic surgeons along conservative lines has helped many patients. Then more radical procedures, such as arthrodesis,[61] were tried, and they proved their worth by the cure of many patients with stubborn sciatica. Now neurosurgical procedures are taking their place in the treatment of this common and incapacitating disorder. As early as 1911 Middleton and Teacher [62] described pressure on the spinal cord by protrusion of the intervertebral disk, but it was considered a rare condition. Not until 1937 was it clearly demonstrated, by Barr and Mixter,[63]

61. Smith-Petersen, M. N., and Rogers, W. A.: Arthrodesis for Tuberculosis of the Sacro-Iliac Joint: Study of End-Results, J. A. M. A. **86**:26 (Jan. 2) 1926.

62. Middleton, G. S., and Teacher, J. H.: Glasgow M. J. **76**:1, 1911.

63. (*a*) Barr, J. S.: J. Bone & Joint Surg. **19**:323, 1937. (*b*) Mixter, W. J.: Ann. Surg. **106**:777, 1937. (*c*) Barr, J. S.; Hampton, A. O., and Mixter, W. J.: Pain Low in the Back and "Sciatica" Due to Lesions of the Intervertebral Disks, J. A. M. A. **109**:1265 (Oct. 16) 1937.

that a certain number of cases of "sciatica" are caused by this lesion in the lumbar portion of the spine. Pain, starting in the back and spreading down the thigh and outer side of the leg, even in the ankle, is the presenting symptom. The pain is severe and lancinating and is brought on by bending and lifting. There is limitation of motion of the lower part of the back and in extension of the affected leg. The ankle jerk on this side may be diminished or absent. Sometimes roentgenograms show narrowing of the intervertebral disk, and three fourths of the patients have a slightly increased protein content of the spinal fluid. Diagnosis, however, is not certain until iodized poppyseed oil has been injected into the lumbar sac of the spinal canal and roentgenograms have finally demonstrated the lesion.[64] If the diagnosis seems certain, laminectomy is performed, and usually a mass is found protruding into the spinal canal between the fourth and the fifth lumbar vertebra. The annulus of the disk has ruptured and made a tumor which presses on some of the roots of the sciatic nerve. In some cases the nucleus pulposus of the disk protrudes through the ruptured annulus, making a chalky, fibrous mass. Removal is not difficult if proper exposure can be obtained without trauma to the nerve structures. Mixter [63b] reports 58 cases of intractable pain in the back; in none of these cases had conservative orthopedic treatment given relief. Diagnosis of rupture of the intervertebral disk was made, and all the patients were subjected to operation. In 32 cases the symptoms were relieved, often immediately; in 14 other cases there was marked improvement. Thus it seems that another vague neurologic entity, "sciatica," is being split up into its elements by careful research, and on the basis of knowledge concerning its causation rational therapy is being administered.

64. Hampton, A. O., and Robinson, J. M.: Am. J. Roentgenol. **36**:782, 1936.

Book Reviews

Clinical and Experimental Investigations in Agranulocytosis. By Preben Plum, M.D. Pp. 410, with 125 illustrations and 42 tables. Copenhagen: Nyt Nordisk Forlag, 1937.

This is an excellent piece of work, which was carried on while the author was working as a research fellow under Prof. Valdemar Bie at the Blegdam Hospital in Denmark. It represents an unusually comprehensive study of agranulocytosis based on a careful review of the literature and on 88 cases, all but 1 of the patients coming under the author's observation.

The monograph is a scholarly production. Every detail has been well worked out. The history of agranulocytosis is interestingly gathered together. The clinical description of the disease and its differential diagnosis are clear, logical and concise. The discussion of the possible etiology of the condition is especially interesting. The author argues a strong case against aminopyrine and presents striking figures to show the close parallelism in Denmark from 1926 to 1936 between the sale of aminopyrine, on the one hand, and the number of known cases of agranulocytosis, on the other. He thinks, in the light of present knowledge, that the best form of treatment available is that of prevention; the best prophylaxis is reduction of the use of drugs which appear to injure the formation of leukocytes.

Students of hematology will appreciate the colored and uncolored photographs of marrow and blood films which have been reproduced. They illustrate the author's conception of the type of cell encountered in studies of the bone marrow and demonstrate the practical value of this particular diagnostic method.

The translation of this book into English was done by Dr. Hans Andersen. He deserves a compliment for the felicitous manner in which he has presented Danish points of view and concepts to English readers.

Last, but not least, the author appears to be a level-headed investigator with a knack at digesting and evaluating the work of others. His bibliography of 422 recent references to the subject bears witness to his thoroughness. On the whole the volume can be highly recommended to any reader at all interested in diseases of the blood.

Fever Therapy. Edited by the Members of the American Committee. Pp. 486. New York: Paul B. Hoeber, Inc., 1937.

As long ago as 1931 an American conference on fever therapy was held in Rochester, N. Y. Other conferences were held each year thereafter and proved interesting. Finally it was decided to hold an international conference on the subject. This took place in New York on three days in March 1937. Physicians from sixteen countries were in attendance. The present volume records abstracts and discussions of the papers presented at that meeting.

The book is not as large as it appears as it is really only 184 pages long. Each abstract, however, is reprinted in English, French and German. The abstracts of the various papers reported are by necessity short, but from them and the ensuing discussion one can obtain at a glance a good deal of information concerning the present international status of fever therapy.

Fever therapy is being employed in a number of diseases, beneficially in some and without obvious benefit in others. Syphilis and gonorrhea, for example, appear often to be benefited by heat, whereas multiple sclerosis does not. The discussions of the various papers are interesting for they show where doubt exists, and one gathers that overenthusiasm is being curbed. On the whole this is an interesting volume worth having in any medical library. It makes a useful handbook for reference.

Approved Laboratory Technic: Clinical, Pathological, Bacteriological, Mycological, Parasitological, Serological, Biochemical and Histological. By John A. Kolmer, M.D., and Fred Boerner, V.M.D. Second edition. Price, $8. Pp. 893, with 392 illustrations. New York: D. Appleton-Century Company, Inc., 1938.

The text constitutes an encyclopedia of laboratory procedures and has an enormous scope. Besides covering all clinical laboratory procedures, it discusses the housing, feeding, inoculating, bleeding and autopsy study of animals and the prevention and the emergency treatment of laboratory accidents. The second edition has been thoroughly revised and brought up to date. Five new chapters have been added: on methods for the hormonal diagnosis of early pregnancy, hydatidiform mole, chorionepithelioma and teratoma of the testes; on diagnostic mycologic methods; on methods of examination of the skin and mucous membranes for animal parasites; on methods for conducting tests for allergy, and on histologic methods and the preparation of specimens for museums. The new chapter on mycology and the increased amount of material devoted to parasitology are to be welcomed. The chapters devoted to bacteriologic and serologic procedures are especially fine. The illustrations are plentiful and well chosen. In this edition the new colored plates on normal and abnormal blood cells are a definite improvement. The reviewer deplores the almost complete lack of a bibliography in a text of this type, which is, in reality, a compilation of laboratory procedures. An "approved" list of additional references at the close of each chapter, such as that given by Konzelmann after the chapter entitled "Histological Methods and the Preparation of Museum Specimens," would add even greater value to the book.

The book should be invaluable to clinical pathologists, to laboratory technicians and to the practicing physician who must do or supervise his own laboratory work. The absence of discussion of the clinical significance and diagnostic value of the laboratory tests described limits greatly its value as a text for medical students.

Le traitement radiologique de l'actinomycose. By Axel Renander. Price, 8 kroner. Pp. 75. Stockholm: P. A. Norstedt & Söner, 1937.

This excellent summary of the radiologic management of actinomycosis describes the results of treatment of 52 patients observed since 1915 in Radiumhemmet, in the Roentgen Institute of the Serafimer Hospital and in the private practice of Dr. G. Forssell. The following lesions were encountered: those of the face and neck in 31 patients, of the abdomen in 13, of the thorax in 3, of the skin in 2, of the genital region in 1 and of undetermined origin in 2. The form of treatment has varied, but currently it consists of roentgen therapy, the application of molded plaques containing radium needles or exposure to a radium bomb, or *téleradium*. In this series of cases these various technics were employed singly or in diverse combinations. Roentgen therapy was effected by repeated exposures, totaling one skin erythema dose, daily or on alternate days over a period of from three to twelve days. The intervals between such series was six to eight weeks, and as many courses as necessary were given. The tube, which was operated at 160 to 170 kilovolts, and filters of various sorts were used. The amount of radium applied in the plaque varied from 200 to 1,600 milligram hours but was usually enough to cause a light erythema with some desquamation. The maximum amount of radiation applied by means of the bomb was 56.22 gram hours, although most patients received much less.

The following results were obtained with this treatment: Twenty-one of the patients with actinomycosis of the face and neck were cured; 5 of those with abdominal involvement and both patients with cutaneous lesions recovered. The author demonstrates adequately the value of vigorous roentgen and radium therapy but was unable to state which technic was the more efficacious. It appeared that the traditionally used potassium iodide did not alter appreciably the radiologic results.

The Diary of a Surgeon in the Year 1751-1752. By John Knyveton, Licentiate of the Society of Apothecaries; Doctor of Medicine of the University of Aberdeen; Teacher of Midwifery to Man and Mid-Wife in Infirmary Hall; Surgeons' Mate, H. M. S. Lancaster. Edited and transcribed by Ernest Gray. Cloth. Price, $2.50. Pp. 322, with 9 illustrations from contemporary sources. New York: D. Appleton-Century Company, 1937.

This is a delightful book and may be read with a great deal of pleasure not only by the doctor but by any one who cares for early works. The easy flowing style, the miniature word paintings and what the publisher calls a Pepysian flavor add to the charm. One might suspect a familiarity with Pepys were it not for the fact that John Knyveton died while Pepys' journal was still lying about undeciphered.

Nothing much is added to the knowledge of medical history, for physicians are already familiar with the history of the period, but the breezy style and the youthful optimism of the presentation supply a novel vantage point from which to view the period. One of the bright spots of the book is where William Hunter is described as "having a damnable way of never Offering a Suggestion on matters Medico-Physical until he has proved it privately by Experiment beforehand; the which is Highly Exasperating to those that prefer to browse on the Windy Heights of Pure Discourse."

The author recounts his student days, with comments on the activities of the resurrectionists, the bleedings, the clysters, the "laudable pus," the puerperal sepsis and all the things that blessed and cursed this period of medical practice. He dwells a bit on the nonmedical diversions of the medical students of the time.

In connection with his experience as surgeon's mate in the British navy, he discusses scurvy, the treatment of gunshot wounds and injuries aboard ship. He took part in an attack on a pirate ship. Later he was placed in medical charge of an island overrun with yellow fever and became a victim of the disease, but survived.

There was never a dull moment in his life, and the book will entertain all the members of the reader's family and will perhaps mildly shock some of them.

Uric Acid in Blood and Urine. By Knud Brøchner-Mortensen. Price, 9 kroner. Pp. 269, with 63 tables, 58 diagrams and 45 protocols. Copenhagen: Levin & Munksgaard, 1937.

This is an excellent piece of work, done, apparently, by the author in connection with his thesis for the degree of Doctor in Medicine at Copenhagen. First written in Danish, it is now printed in English, only the final chapter appearing in both languages. The tables and diagrams which accompany the discussion are easily understood. The translation from Danish to English is admirable.

The author first reviews various methods available for the analysis of the uric acid in blood and urine and points out their most striking faults. Finally he presents new methods of his own devising and describes the technic of their performance in detail.

After a historical account of methods, the remainder of the book is concerned with experiments in which the new methods were utilized. The experiments dealt with uric acid clearance under a variety of circumstances, under conditions in which the purin or the protein content of the diet or the rate of water excretion was varied widely. A final chapter summarizes the monograph. Tables are appended in which are recorded the protocols of the observations which were made. Last of all is an excellent bibliography.

A glance through the bibliography reveals strikingly evidence of how much important work in later years has been done by American biochemists and physiologists on problems of uric acid metabolism. This thesis will be of chief interest to investigators in that particular field.